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Diagnostics of central nervous system metastatic disease

KEYWORDS: Central Nervous System Neoplasms; Spinal Neoplasms; Neoplasm Metastasis; Diagnostic Imaging; Magnetic Resonance Imaging; Tomography, X-Ray Computed

Ten to 50% of patients with systemic malignancy develop brain metastases during the course of their disease and metastases account for more than half of all brain tumours in adults. The major originating primary tumours are carcinomas typically arising from following sites: lung, breast, unknown primary, melanoma, colorectal and others. The majority of patients have multiple metastases.

The diagnosis of brain tumours should be suspected in any cancer patient who develops any new neurological symptoms. Brain metastases present with headaches in 40%-50% of patients, with increased frequency with multiple metastases or posterior fossa metastases. Seizures and behavioural symptoms are also common while, in contrast, focal neurological signs are rare as presenting symptoms.

In patients suspected to have brain metastases, contrast enhanced magnetic resonance imaging (MRI) is the best diagnostic test. However, computed tomography (CT) remains initial modality of investigation. If the CT scan shows multiple metastases then an MRI would not usually add any further information. However, in good performance status patients, if a single metastasis is seen on CT imaging, an MRI should be performed to exclude multiple metastases before more radical treatment.

The imaging appearance of metastatic lesions is highly variable, depending upon tumor type, the presence of hemorrhage, cystic change and necrosis. Edema is usually extensive due to lack of a blood brain barrier. Hemorrhage is seen in approximately 20% of metastatic lesions, most commonly in malignant melanoma, lung, breast and renal cell carcinoma. Although multiplicity is the hallmark of metastatic disease, almost half of patients have a solitary metastases at the time of diagnosis in some series. Most report a 60%-70% incidence of multiplicity, however. Lesions occur most commonly in the middle cerebral artery distribution, concentrated in the watershed zones and at the gray/white matter junction. Although a majority of lesions occur in the cerebrum, posterior fossa lesions are seen in 15% to 20%, with rare occurrences in the brain stem, pineal region, and parasellar regions.

On CT images, metastatic lesions may be hypo-, iso- or hyperdense. Moderate to severe perifocal edema is present. Calcifications are rare prior to therapy. Following contrast administration, intense enhancement is noted, which may be solid or rim-like in distribution.

MR images better characterize the variable tumor constituents. Hemorrhage and other paramagnetic substances, necrosis, and other pathologic features are well delineated. Gadolinium-enhanced, T1-weighted images are the most sensitive sequence for the detection of metastases, and may be positive even prior to the appearance of abnormalities on long TR images if sufficient perifocal edema or mass effect have not yet developed. This is especially true if the lesions are subarachnoid, rather than parenchymal.

On diffusion-weighted MR imaging (DWI) signal intensity of nonnecrotic components of metastases is variable (iso- or hypointense; occasionally hyperintense). The necrotic components of metastases show a marked signal suppresion on DWI and increased ADC values on ADC maps. This may be related to increased free water and/or presence of extracellular methemoglobin and/or increased viscosity. The increased signal intensity on DWI and low ADC are unusual but possible.

MR Spectroscopy could add valuable information in differentiating primary neoplasm from metastasis: absent or practically absent NAA and Cr levels are suggestive of a metastatic lesion. Furthermore, if the spectral analysis of the peritumoral region shows an increase in Cho level, it is probably an infiltration related to primary neoplasm. If there is no elevation in Cho level, it is probably vasogenic edema associated with metastases.

The spine is the third most common site for cancer cells to metastasis, following the lung and the liver. Approximately 60%-70% of patients with systemic cancer will have spinal metastasis; fortunately, only 10% of these patients are symptomatic. About 94%-98% of these patients present with epidural and/or vertebral involvement. Intradural extramedullary and intramedullary seeding of systemic cancer is unusual; they account for 5%-6% and 0.5%-1% of spinal metastases, respectively.

Spinal metastases are a common consequence of malignant disease and approximately 10% of patients with cancer will develop spinal cord compression (SCC). Bony spinal metastases can arise from any primary malignancy but occur commonly from prostate, breast, and lung cancer. Other less common causes are renal cell carcinoma, multiple myeloma, and non-Hodgkin's lymphoma.

Spinal metastases without neurological compromise are more common than SCC, though 20% of patients with spinal metastases will develop SCC. One fifth of cases of SCC present in patients without a known primary site.

Two thirds of SCC are in the thoracic region because of the narrower spinal canal. SCC presents with pain in over 80% of patients and often develops over 7-15 weeks before the onset of neurological symptoms. Motor weakness is present in 60%-85% of patients with SCC, usually producing bilateral leg weakness. Sensory signs are less common than motor weakness, often with a sensory level, but can occur in a radicular distribution, with ascending numbness or paresthesia. Bowel and bladder disturbances are late features but may develop in up to 50% of patients.

Neither the site of pain nor the sensory level often correlate with the actual level of cord compression. Unfortunately, because of delay in presentation and diagnosis malignant SCC is a significant cause of morbidity and mortality.

The investigation of choice is an MRI scan of the spine, as plain radiography and isotope bone scans are inadequate for diagnosis and predicting the level of compression.

Plain radiography is used to show erosion of the pedicles or the vertebral body. Owl-eye erosion of the pedicles in the anteroposterior (AP) view of lumbar spine is characteristic of metastatic disease and is observed in 90% of symptomatic patients. However, radiologic findings become apparent only when bone destruction reaches 30%-50%. Osteoblastic or osteosclerotic changes are common in prostate cancer and Hodgkin disease; they are occasionally seen in breast cancer and lymphoma.

CT scanning is useful in determining the integrity of the vertebral column, especially when surgery is anticipated. CT myelography is used if MRI is not available. CT also allows for an examination of paraspinal soft tissues and paraspinal lymph nodes (Figure 1).

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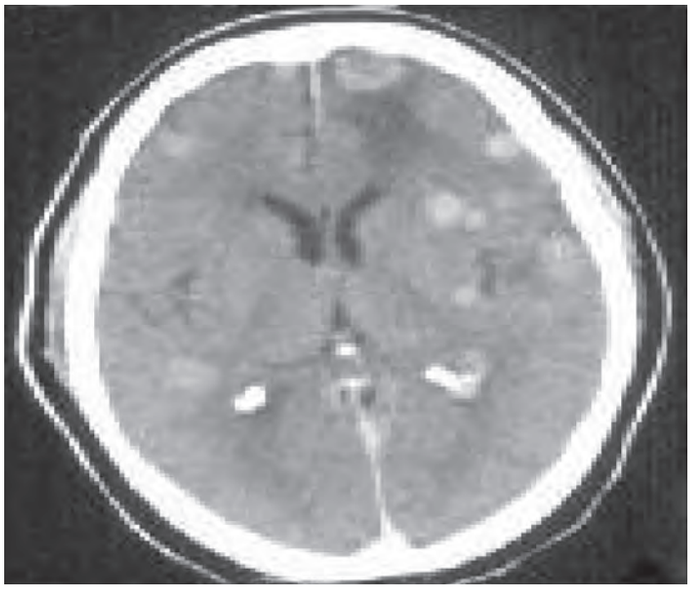

Figure 1. CT: Multiple metastasis in a patient with colon cancer. Contrast-enhanced CT scan

Myelography is still used in situations where MRI is not available. CSF sampling should be deferred if evidence of near-complete or complete spinal block is noted. The risk of neurologic deterioration after myelography is about 14% but less likely than this with C1-2 puncture.

MRI is the imaging modality of choice. Contrast-enhanced fat-suppressed images help to differentiate metastasis from degenerative bone marrow. Diffusion-weighted images distinguish metastasis from osteoporotic bone. Osteoporotic fractures are hypointense, and metastases are hyperintense.

Metastatic disease to the neuraxis other than the brain parenchyma and the spinal column is uncommon. The incidence of cancer cells invading the leptomeninges is as high as 8%-13%. In autopsy studies, the rate has been estimated to be 25% (Figure 2).

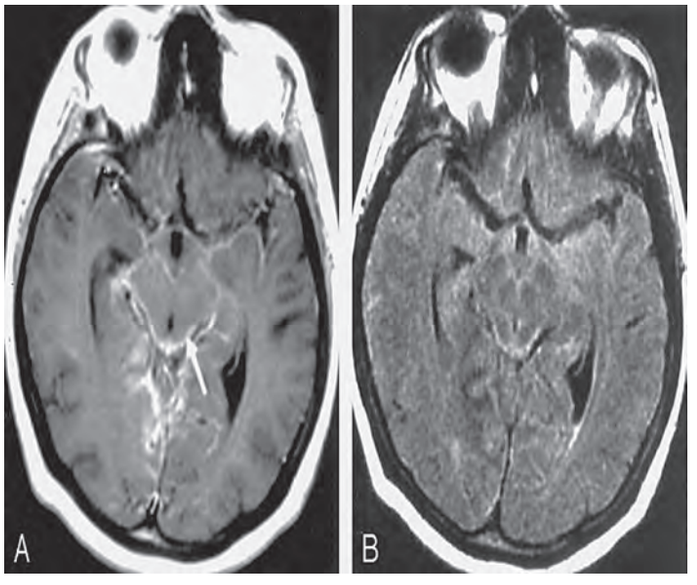

Figure 2. MRI: Leptomeningeal metastasis in a patient with breast cancer. A) Postcontrast T1W axial image B) Axial FLAIR sequence

Meningeal disease occurs in 5% of patients with cancer. Usually these patients have advanced disease at other sites and 50% have had brain metastases treated previously. Common causes of meningeal metastases are haematological malignancies, lung cancer, breast cancer and melanoma.

Meningeal disease caused by non-haematological tumours is associated with a median survival time of only three months. Treatment is often ineffective for a number of reasons; the main difficulty is delivering chemotherapy agents to the malignant cells in the central nervous system (CNS), and as meningeal disease presents as a late complication of malignant disease the general prognosis is poor.

The types of clinical features can be divided into three subgroups: (1) cerebral (cognitive impairment, headache, nausea and vomiting, and ataxia); (2) cranial neuropathies; and (3) spinal (back pain, radiculopathies). These particular symptoms are produced by the tendency of malignant cells in the cerebrospinal fluid (CSF) to congregate in specific sites: base of skull producing cranial neuropathies, obstruction of CSF flow, and raised intracranial pressure (ICP); base of spine producing back pain, leg weakness, radiculopathies, bowel/bladder disturbance (Figure 3).

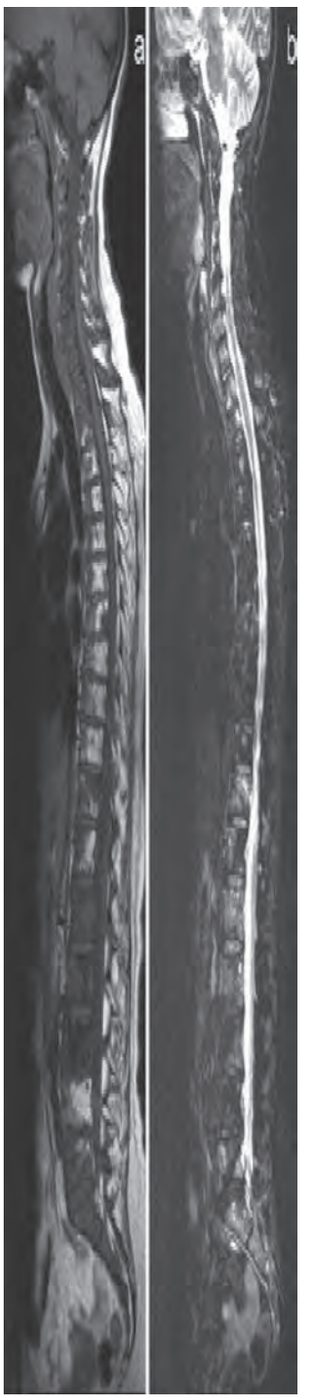

Figure 3. MRI: Diffuse metastatic infiltration of the whole spine, predominantly of the cervical and lumbar region, in a patient with breast cancer. a, b Sagittal T1-weighted and STIR images

These areas are the most commonly identified radiologically and at postmortem examination, and is possibly caused by the effect of gravity and slow flow of CSF.

The gold standard for diagnosis is the identification of malignant cells in the CSF. MRI can provide definitive evidence of meningeal disease though its sensitivity and specificity are yet to be established.

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Anaesthesia and resuscitation of the patients with metastatic brain disease

KEYWORDS: Brain Neoplasms; Neoplasm Metastasis; Cardiopulmonary Resuscitation; Neurosurgical Procedures; Anesthesia; Clinical Protocols; Ethics, Professional

Metastatic tumors

Metastatic lesions change dramatically intracranial dynamics. Initially, when the tumor is small and slowly enlarging, volume-spatial compensation occurs by compression of the cerebrospinal fluid (CSF) compartment and neighboring cerebral veins, which prevents increases in intracranial pressure (ICP). However, as the lesion expands, compensatory mechanisms are exhausted and further increase in tumor mass causes progressively greater increase in ICP.
As the metastatic tumor expands, it can outgrow its blood supply, developing a central zone of hemorrhage that may enlarge rapidly, increasing ICP. Surrounding brain edema increases the effective bulk of the tumor and represents an additional portion of the brain that looses its autoregulating function. In such situations of compromised intracranial compliance, small increases in arterial pressure may produce large increases in cerebral blood flow (CBF), which can substantially increase intracranial volume and ICP with the subsequent complications (1).

Treatment of brain metastases

Because few patients with brain metastases will be cured definitely, the aim of treatment is to control neurological dysfunction and not worsen the patients' quality of life. Left untreated, the persons with brain metastases have a median survival of 1 month, and the cause of death is often attributed to the brain tumor(s) itself (2). Treatment options range from no treatment, symptomatic and supportive treatment with medications, and definitive therapies such as: surgery, radiotherapy, chemotherapy, hormonal therapy, or a combination of these. With improvements in neurosurgical techniques and newer technologies in radiotherapy, more options for the treatment of brain metastases have arisen. Figure 1 displays a decision tree of treatment possibilities for brain metastases (3).
In general, for all patients with newly diagnosed brain metastases, corticosteroids are promptly started resulting in neurological improvement within 48 hours in at least two thirds of patients (4,5). After a bolus of 12 to 24 mg, patients are placed on 8 mg of dexamethasone four times daily. For patients with life-threatening brain herniation, the steroid dose may be enlarged to 16 mg four times daily, after an initial bolus of up to 48 mg (6). The exact mechanism for the action of corticosteroids is not fully understood but is thought to decrease tumor capillary permeability and promote extracellular fluid absorption (4). The neurological improvement after steroid treatment is mostly due to a decrease in peritumoral edema, and not a consequence of any direct action on the tumor cells. The median survival time for patients with brain metastases who only receive steroid therapy is twice longer, being approximately 2 months (2). There are serious side effects occurring with some patients on long-term corticosteroid treatment. Corticotropin-releasing factor (CRF) has been studied as an alternative drug as effective as steroids, but with fewer side effects (7).
Patients who present with focal or generalized seizures will also be treated with anticonvulsants.
It has been suggested that phenobarbiton, phenytoin, carbamazepine, and valproic acid are all equally effective as first-line agents in controlling seizures (2).

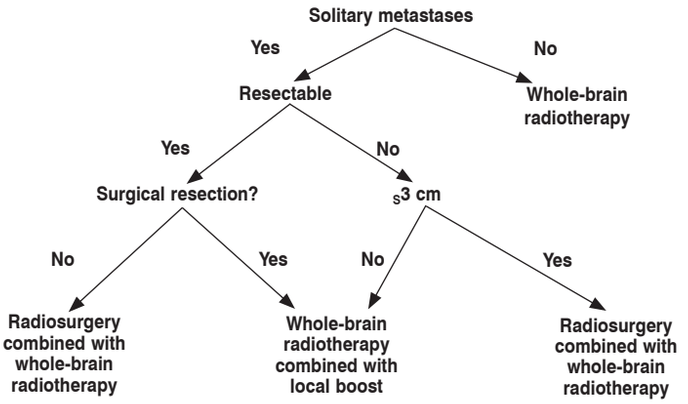

Figure 1. A decision tree of treatment options for brain metastases

Anesthetic techniques and drugs

The aim of neuroanesthetic care for patients with metastatic tumors is to reduce intracranial volume. ICP must be under control before the cranium is opened, and optimal operating conditions obtained by producing a small, elastic brain that facilitates surgical dissection. Various procedures and pharmacologic agents have been used to reduce brain bulk (Table 1). The application of these methods selectively or together is often accompanied by significant clinical improvement. In acute states of intracranial hypertension, good oxygenation with mechanical hyperventilation provides the basis of neuroresuscitative care.

Table 1. Clinical control of intracranial hypertension

Adequate oxygenation
Hyperventilation
Diuretics: osmotic, loop (tubular)
Corticosteroids
Position to improve cerebral venous return
Anesthetic agents (thiopental, propofol, etomidate)
Blood pressure control
Fluid restriction
Hypothermia

Premedication

Lethargic patients receive no premedication. Patients who are alert, but anxious, may receive an anxiolytic (e.g., diazepam or midazolam, 0.1 mg/kg i.m.) before coming to the operating room. If there is any doubt about the patient's

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level of consciousness, the patient may be given sedation or analgesics in the operating room after an intravenous route is established. An anticholinergic drug (atropine sulphate) is readily administered preoperatively, in a dose of 0.4-0.6 mg i.m., 45-60 minutes before induction of anesthesia – to diminish secretions and decrease possibility of life-threatening bradycardia (8).

Control of intracranial hypertension

Rapid brain dehydration and ICP reduction can be produced by administering diuretics. Two diuretics are in use: the osmotic diuretic mannitol and the loop diuretics: furosemide and bumetanide. Mannitol is given as an intravenous infusion in a dose of 0.25-1.0 g/kg. Its action begins within 10-15 minutes and is effective for approximately 2 hours. Larger doses produce a longer duration of action but do not necessarily reduce ICP more effectively. Furthermore, repeated administration can result in metabolic derangement. Mannitol is only effective when the blood-brain barrier is intact. When the blood-brain barrier is disrupted, mannitol may enter the brain and increase osmolarity. Mannitol could pull water into the brain as the plasma concentration of the agent declines and cause a rebound increase in ICP. This rebound increase in ICP may be prevented by maintaining a mild fluid deficit (9).

Hypertonic agents such as mannitol should be administered cautiously in patients with preexisting cardiovascular disease. Furosemide or bumetanide may be better agents to reduce ICP in patients with decreased cardiac reserve.

The loop diuretics furosemide and bumetanide reduce ICP by inducing a systemic diuresis, decreasing CSF production, and improving cellular water transport. However, they are not as effective as mannitol in reducing ICP. Furosemide can be given alone as a large initial dose (0.5-1 mg/kg) or as a lower dose with mannitol (0.15-0.30 mg/kg). A combination of mannitol and furosemide diuresis has been shown to be more effective than mannitol alone in reducing ICP, but causes more severe dehydration and electrolyte imbalances.

Hyperventilation to a $PaCO_2$ of 25-30 mm Hg is the cornerstone of management of intracranial hypertension. Hyperventilation reduces brain volume by decreasing CBF through cerebral vasoconstriction. For every 1 mm Hg change in $PaCO_2$, CBF changes by 1-2 mL/100 g/min. The duration of effectiveness of hyperventilation for lowering ICP may be as short as 4 to 6 hours, depending on the pH of the CSF. Hyperventilation is only effective when the CO_2 reactivity of the cerebral vessels is intact. Decreased responsiveness to changes in CO_2 tension occurs in areas of vasoparalysis, which are associated with extensive intracranial disease such as metastatic tumor is.

Perioperative fluid maintenance in the routine neurosurgical patient is provided with glucose-free, isoosmolar crystalloid solutions to prevent increases in brain water content. Blood loss is replaced by crystalloid and colloid solutions, at approximately a 3:1 ratio (crystalloid:colloid) down to a hematocrit of approximately 25%-30% depending on the patient's physiologic status. Only when the hematocrit is severely decreased, under 20%-25%, packed red cells and fresh frozen plasma are used for volume restoration.

The administration of anesthetic agents that increase cerebral vascular resistance can acutely reduce ICP. Thiopental, propofol, and etomidate are potent cerebral vasoconstrictors that can be used for this purpose. These agents are usually administered during induction of anesthesia, but may also be administered in anticipation of noxious stimuli or to treat persistently elevated ICP in the intensive care unit.

Although rarely used to reduce ICP, hypothermia does this by decreasing brain metabolism, CBF, cerebral blood volume, and CSF production. Drugs that centrally suppress shivering, muscle relaxants, and mechanical ventilation are required when hypothermic techniques are employed. Intraoperatively, a modest degree of hypothermia, approximately 34˚C, is recommended.

Induction, maintenance, and emergence

When the patient is brought into the operating room, osmotherapy may be indicated before induction of anesthesia. After appropriate monitoring devices are applied, preoxygenation of the patient is provided. Before laryngoscopy and intubation of the trachea, the patient is smoothly and deeply anesthetized with agents that reduce ICP. In the presence of elevated ICP, thiopental is an agent of choice to induce anesthesia; however, alternative agents such as propofol, etomidate, or midazolam can be used depending on the patient's medical condition. Endotracheal intubation is performed as rapidly and smoothly as possible. After induction of anesthesia, ventilation of the lung is controlled mechanically and adjusted to maintain $PaCO_2$ between 25 and 30 mmHg.

The most commonly administered maintenance anesthetics for patients with metastatic tumors are nitrous oxide-opioid and nitrous oxide-volatile inhalational agents. In practice, the opioid most frequently employed is fentanyl, and the volatile agents most frequently employed are isoflurane or sevoflurane. Nitrous oxide, 50%-70% in oxygen, is typically administered to decrease the total dose of intravenous agent or the required concentration of volatile agent. The cerebrovascular effects of nitrous oxide are not benign, and studies report that at equipotent doses, isoflurane has less adverse effects on ICP and CBF than nitrous oxide. Therefore, in the presence of new, technologically improved anesthesia machines, administration of nitrous oxide is avoided and oxygen:air mixture is used instead.

When severe intracranial hypertension exists and the brain is tight despite adequate hyperventilation and the administration of steroids and diuretics, a totally intravenous technique is recommended. For example, a propofol infusion (50-200 μg/kg/min), and fentanyl boluses or infusion (1-4 μg/kg/h), can be administered in cases of severe intracranial hypertension (10).

Emergence from anesthesia should be as smooth as possible, avoiding straining or bucking on the endotracheal tube. Bucking can cause arterial hypertension and elevated ICP during termination of anesthesia, which can lead to postoperative hemorrhage and cerebral edema. To avoid bucking during emergence, muscle relaxants are not reversed until the head dressing is applied.

In the usual craniotomy for excision of a metastatic tumor, the anesthetic plan is aimed at awakening and extubating the patient at the end of the procedure. The patient is extubated only when fully reversed from muscle paralysis, and when he is awake and following commands. A brief neurological examination is performed before and after extubation of the trachea. The patient is positioned with his head elevated 15˚- 30˚ and transferred to the intensive care room with oxygen by mask and oxygen saturation monitoring. Close monitoring and care, including frequent neurological examinations, is continued in the intensive care room.

Postoperative care

There are three concepts used as the contemporary treatment options, depending on an overall physical condition and a short-term prognosis of a patient with metastatic brain disease:

1. palliative care – for cachectic, soporous, uncooperative patients with hopeless short-time prognosis: good nursing, sufficient medication for pain and other symptoms, intravenous hydration only when it provided relief for patient's symptoms;
2. active care – for somnolent, but cooperative patients with relatively good short-time prognosis: use of antibiotics, intravenous hydration or blood transfusions aimed at saving the patient's life in a life-threatening condition;
3. intensive care – for alert, fully cooperative patients, in relatively good physical condition with quite good short-time prognosis: referring the patient to intensive care unit (ICU).

Terminal care – to resuscitate or not?

One of the difficult dilemmas in terminal care is the decision on whether to start or withhold cardiopulmonary resuscitation (CPR). Is this decision made on purely medical basis, or is it also influenced by the physician's personal characteristics or education (11)?

Recent advances in medical technology provide more powerful cures for diseases, and in this way, prolong and improve the quality of life. On the other hand, in the case of terminally ill and dying patients, the extension of life may

mean prolonged suffering and misery rather than an improved quality of life. The futility of medical treatment is, indeed, a topical concern in the debate on medical ethics, particularly in terminal care (12-17). There are also financial reasons why physicians today have to reconsider their priorities in health care. Huge resources are invested in terminal care, and health care organizations are required today to show results in this area as well (18,19).

The problem of withholding or withdrawing treatment is particularly acute in the context of terminal care (20). Opinions are divided on the withholding of cardiopulmonary resuscitation (CPR) in the case of terminal cancer patients (13,17,21-23). Guidelines have been published describing the procedures that should be followed when orders are issued for non-resuscitation and to set out the clinical, legal, and ethical criteria that should be satisfied before such orders are issued (24). However, we do not have any specific guidelines for resuscitation decisions in Serbia.

Clinical decision-making involves complex interaction among many different factors. One of the most extreme cases is the sudden death of a terminal patient. Usually, active treatment with CPR is started immediately; but what will physicians do in the case of a terminal cancer patient depends on many factors. Partly, a physician's decision is made purely on medical basis and current guidelines, and partly on his personal views and characteristics. Or, ultimately, is the doctor's decision determined by his/her training and education (25-29)?

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Surgical therapy for brain metastases

KEYWORDS: Brain Neoplasms; Neoplasm Metastasis; Surgery; Postoperative Care

GENERAL CONSIDERATIONS

Brain metastases are the most common problem in neuro-oncology and they represent 50% of all intracranial tumors (1). The incidence of metastatic brain tumors in one year is 3 to 11 on 100.000 populations. However, according to autopsy series the probability of developing brain metastases from a primary tumor site is 25% of all cancer patients (2). They outnumber the primary brain tumors almost ten times (3). Intracranial metastases can be located in the skull bones, brain parenchyma or can infiltrate dural and/or leptomeningeal coverings of the brain. The majority of patients with brain metastases are 50 to 70 years old (about 60%) (1).
In 20% of patients symptomatic brain metastases are the first sign of malignant disease. Incidence of the multiple metastases seems to be greater than previously thought, occurring in up to 60% to 75% of patients (4). Metastatic cancer of an unknown primary lesion accounts for 3%-5% of all cancers, and makes it the seventh most common malignancy. About 15% of brain metastases are included in this category.

Signs and symptoms of brain metastases

As any other intracranial tumor, brain metastases can develop signs and symptoms of the raised intracranial pressure (headache, nausea, vomiting, seizure, papilledema, mental changes), or focal sings and symptoms depending on the location of the metastatic tumor (motor weakness, balance problems, speech disturbances).
The relative distribution of brain metastases tends to occur in a pattern proportional to the blood flow to specific brain areas. Almost 85% of all metastases are located in the cerebral hemispheres, and only 10% to 15% in cerebellum and 2% to 3% in brain stem (5). About 10% of patients present with intramural hemorrhage.

Diagnostic procedures

The most important diagnostic procedures are computerized tomography (CT) and magnetic resonance imaging (MRI) of the brain. The sensitivity of the last one is much greater than the first one, because it can demonstrate lesions less than 1 cm in diameter. In some diagnostically unclear cases MRI spectroscopy can determinate the nature of the multiple or solitary lesions in the brain.

Differential diagnosis of metastatic brain disease

Solitary lesions with MRI spectroscopy do not represent diagnostic problem any more. However, multiple intracranial lesions do not necessarily have to be metastatic ones. Actually, in 11% of patients with malignant diseases multiple intracerebral lesions are not metastatic. They are usually multiple abscesses (20%), especially in patients with immunodeficiency syndromes. In patients with unknown primary malignant disease they can be granulomas (usually due to systemic sarcoidosis), acute disseminated demyelinating disease, progressive multifocal leukoencephalopathy or postirradiation necrosis or demyelization. Multiple intracerebral hematomas can mimic brain metastases in patients with coagulopathy.

TREATMENT OPTIONS

Medicamentous therapy

Brain metastases are frequently surrounded with significant edema. The administration of steroids provides some short-term relief of the edema, but additional treatment in necessary. Dexamethasone is the steroid of choice because of limited mineralocorticoid activity and long clinical experience. Starting dose is usually 16 mg daily. Signs and symptoms of intracranial hypertension resolves within two to three days or more, but without any other treatment they develop again after about 4 weeks. An H2 blocker or proton pump inhibitor should be prescribed when high doses steroids are used. Prophylactic anticonvulsants should not be generally prescribed as there has been no proven benefit to their routine long-term use and they have potential side effects. They should be prescribed for short-term use in the perioperative period in high risk patients (tumors in or near eloquent brain, older and/or significantly symptomatic patients or mesial temporal lesions).

Whole brain radiation therapy (WBRT)

WBRT was the first proven effective therapy for brain metastases which has remained the mainstay of treatment for patients with cerebral metastases. The median survival of patients with brain metastases treated with steroids alone is 2 months, and with WBRT extending that survival to 6 months (6). WBRT is most effective after the open surgery for brain metastases. Various WBRT regimens are utilized with the most common regimens ranging 30 to 37.5 Gy in 10 to 15 fractions. Since side effects of these regimens are very common (dementia, ataxia, sometimes urinary incontinency) other WBRT regimens should be performed in patients with longer life expectancy, namely 40 to 45 Gy with daily fractions of 1.8 to 2.0 Gy (1).

Stereotactic radiosurgery (SRS)

SRS utilizes beams of high energy photons to deposit a high dose of radiation to the metastasis with relative little radiation delivered to the surrounding normal brain. There are two main devices for this kind of therapy – gamma knife and modified linear accelerator for SRS. Both machines achieve similar clinical results (7). An SRS dose ranges from 15 to 24 Gy in one single fraction.

OPEN SURGERY FOR BRAIN METASTASES

Two large randomized studies proved that open surgery in solitary brain metastasis with postoperative WBRT significantly prolongs the median survival of the patients (8,9).
In most countries today open surgery with postoperative WBRT is the treatment of choice for solitary brain metastasis. Another study showed that the local control is better after such combined modality treatment (10).
The advantages of open surgery are: (1) total extirpation of the metastasis allows not only the larger level of palliation, but immediately eliminates the effects of

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intracranial hypertension; (2) open surgery provides the pathohistological confirmation of the tumor, which is very important in cases with unknown primary malignant disease; (3) radical operation provides local cure of the metastasis.
The main disadvantage of the open surgery for brain metastases is the possibility of development of the additional neurological and general complications after the operation. Neurosurgical complications are usually the worsening of the preoperatively present neurological impairment, development of intracerebral hematoma, infection etc.
Stereotactic biopsy can only provide the histological diagnosis of the tumor, but it cannot resolve the effects of the intracranial hypertension. It can be performed in clinically unclear cases. The morbidity after stereotactic biopsy is 3%, and the mortality rate is the same. After implementation of neuronavigation, electrocortical stimulation, microsurgery and intraoperative ultrasound postoperative morbidity after open surgery is 10% (only 5% neurological), and the mortality is 0.5% to 3%. Some of recent series reported no mortality after surgery for brain metastases (10,11).

Surgical resection
Selection of patients for surgical resection requires consideration of radiographic (determined by MRI), histological and clinical features.

Radiographic features
Number of tumor lesions. Patients with single brain metastases are the most appropriate surgical candidates, since the surgery in this cases result in longer survival times for these patients compared with other treatments. Patients with single metastases who were treated with surgery and radiation live statistically longer, have fewer recurrences, and had better quality of life than patients treated with WBRT alone (8,9). For patients with multiple metastases the role of surgery is more controversial. It is accepted that if there is one symptomatic large metastatic lesion and multiple small lesions, open surgery for the symptomatic one should be considered with postoperative WBRT (Figure 1).

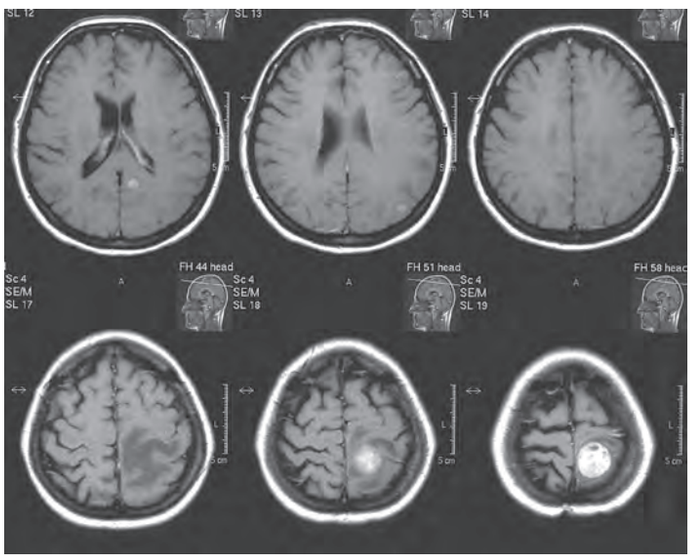

Figure 1. MRI: Multiple metastases from melanoma with two small asymptomatic and one large symptomatic lesion

Tumor size. It has never been shown that tumor size was a factor influencing survival after surgery, but nevertheless, it has become an increasingly important element in decision making because of the potential for treating metastases with SRS. Three groups of patients can be identified according to tumor size. First, there are patients whose tumor is grater than 3 cm (Figure 2).

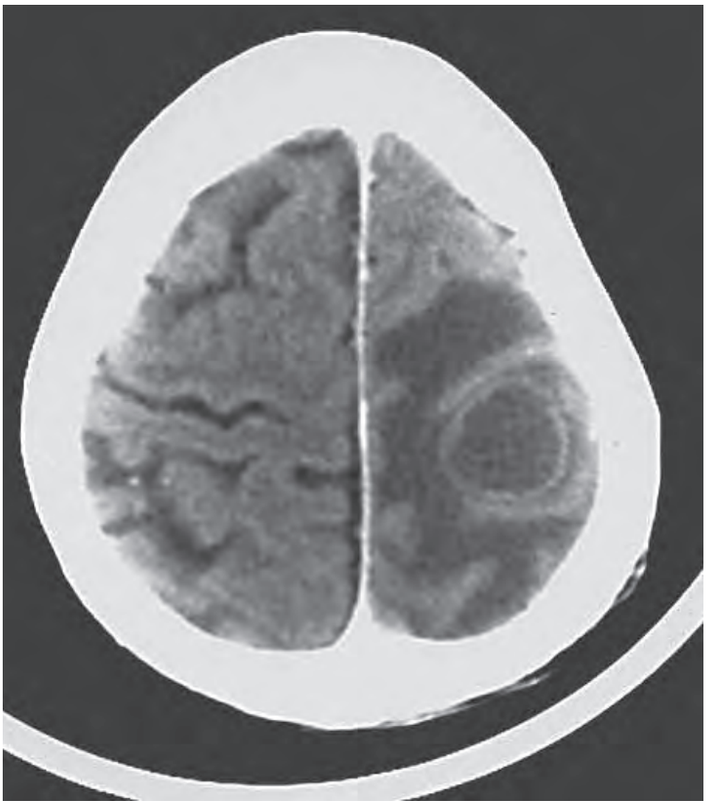

Figure 2. CT: single parietal cystic brain metastasis

For such large tumors surgical resection is the primary and best option. Second, there are patients with very small tumors (less than 5mm in diameter), and for these lesions SRS is most appropriate, particularly if they are located deep within the brain. Last are patients with intermediately sized metastases that typically range from 1 to 3 cm. The decision to operate these lesions is challenging, because in many cases surgery and SRS may be considered equally appropriate treatment methods. However, if metastatic tumor is located in ineloquent part of the brain, open surgery may have some advantage.
Tumor location. If the tumor's location is deep or superficial and if the tumor is within or near the eloquent cortex, it affect the potential for surgery induced postoperative neurological disability. With the modern microneurosurgery, computer – assisted image – guided stereotactic techniques (neuronavigation), intraoperative functional mapping and intraoperative ultrasonography, there is a strong possibility of avoiding postoperative complications. However, lesions that are deeply located are associated with higher surgical morbidity.

Histological features
Tumor histology is significant in treatment decision, because open surgery for brain metastases of radiosensitive primary malignant diseases is contraindicated. Open surgery for single brain metastasis is indicated in primary tumors like melanoma, adenocarcinoma, renal cell carcinoma which are often resistant to radiation therapy, and also for relatively radiosensitive tumors like breast carcinoma, squamocellular lung carcinoma etc.

Clinical features
The most significant determinants of a patient's ultimate outcome are: the status of the systemic disease, the presence of extracranial metastases, general health of the patient with medical comorbidities, the extent of a neurological deficit preoperatively, and the time from first diagnosis of primary cancer to the diagnosis of symptomatic brain metastases (12,13) (Table 1).

Table 1. Indications and contraindications for open surgery due to brain metastases

INDICATIONS	CONTRAINDICATIONS
Single metastases 3 cm in diameter or larger	Multiple small metastases.
Superfitial single lesions in noneloquent parts of the brain (even if there are less than 3 cm in diameter)	
Controlled primary malignant disease	Progressive primary malignant disease
Absence of extracranial metastases	Presence of multiple extracranial metastases
Karnofsky scores of 70 and more	Karnofsky scores less than 70
One large symptomatic and few small asymptomatic lesions	Multiple lesions with one large in brain stem, or basal ganglia
Radioresistant primary malignant tumor	Radiosensitive primary malignant disease
Life expectancy more than 3 months	Life expectancy less than 3 months

Surgical approaches

Surgical approaches depend on anatomic location of the brain metastasis. Supratentorial subcortical lesions are best resected through transcortical approach by an incision in the apex of the involved gyrus. This may be problematic within the eloquent cortex, and in these cases local mapping with direct brain stimulation may minimize the injury to the surrounding brain. Lesions in the subgyral or subsulcal location are best resected through the transsulcal approach by splitting the sulcus leading to the lesion. Lobar metastases deep within the white matter can be resected through both transcortical or transsulcal approaches. Midline and intraventricular supratentorial lesions may be approached by splitting the interhemisphaeric fissure. Cerebellar tumors are best approached along the shortest transparenchymal route to the lesion.

Recurrent metastases

Brain metastases may recur locally or arise at sites other than the original (distant metastases). In appropriate patients reoperation for recurrent brain metastases can improve quality of life and increase survival time (14).

Outcome after open surgery for brain metastases

Surgical mortality is death that occurs within 30 days of operation. Surgical mortality according to recent series is 2% to 4%, or there is no mortality at all. (10,11). It is not higher than stereotactic biopsy or WBRT alone. Postoperative morbidity after surgery includes worsening of neurological deficit and non-neurological complications such as postoperative hematoma, wound infection, deep venous thrombosis, pneumonia, pulmonary embolism etc. In the modern era neurological worsening can be expected to occur in 5% or less of patients undergoing surgery for brain metastases (11,12).

Our one year experiences

During the 2005th year at the Institute of Neurosurgery in Belgrade, 84 patients were operated due to brain metastases. The youngest patient was 34, and the oldest 75 years of age, 50 were males and 34 females. There were 73% patients in sixth and seventh decade of life (more than 60% in other series).

The main feature of our group of patients was that 45% of them were admitted without known primary malignant disease, which is as twice much as in other series. During the hospitalization at the Institute of Neurosurgery, primary lung cancer was confirmed in 8 of these patients (10%). Among operated patients for brain metastasis, 40% had primary lung cancer, 10% breast cancer, 6% previously operated melanoma, 2% colorectal carcinoma, 4% renal cell carcinoma, and 4% cervical carcinoma of uterus. All patients had single metastasis.

Time from the diagnosis of primary disease to the development of symptomatic brain metastases ranged from one month (lung cancer) to 14 years (renal cell carcinoma), with median time of 22 months. Female patients with cervical carcinoma of uterus developed brain metastases usually 5 years after initial diagnosis of primary malignancy. Karnofsky score was more than 70 in 94% of patients, and in the remaining 6% was less than 70 because of severe preoperative neurological deficit. Mortality rate was 2% (both patients had less than 50 Karnofsky score preoperatively), and morbidity rate with transient worsening of neurological status was 5%.

CONCLUSION

With modern microneurosurgical facilities open surgery for brain metastases with postoperative WBRT in well selected group of patients is a safe procedure. It prolongs expected survival time, and improves the quality of life of these patients.

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Pathology of central nervous system metastases – an overview

KEYWORDS: Central Nervous System Neoplasms; Neoplasm Metastasis; Immunohistochemistry; Neoplasms by Histologic Type; Pathology

GENERAL ASPECTS

Metastases of central nervous system (CNS) are common complications of systemic cancers. Because of the neurological disturbances and symptoms of raised intracranial pressure they frequently require prompt therapeutic intervention (1). Metastases usually occur late during the clinical course of a primary tumor. However, they may occur when systemic disease is still occult and quiescent. The CNS may be involved by metastatic deposit both by hematogenous dissemination and by direct extension of primary solid tumors (2,3). In this report we will elaborate the problems of hematogenous CNS metastases.

The incidence of CNS metastases is difficult to estimate due to the diverse sources of analyzed material. The autopsy studies reveal that approximately 24% of adult patients with cancer have intracranial metastases. One third of patients with lung carcinoma develop intracranial metastases and 50% of brain metastases result from this type of cancer (4). Brain metastases are less frequent in children with approximate incidence of 6%. There has been an increase in the incidence of brain metastases in the last decades due to increased patient's survival and owing to the better neuroimaging diagnostic techniques (5).

CNS metastases may develop from any primary systemic neoplasm but some tumors have a predilection for the brain. These are lung and breast carcinomas, followed by melanomas, renal carcinomas and adenocarcinomas of colorectal origin. Increasingly effective management of systemic cancers may account for rising incidence of intracranial deposits from ovarian carcinomas, osseous and soft tissue sarcomas (6,7). The incidence of metastases usually varies according to the histological type of the primary tumor (e.g. adenocarcinoma and small-cell lung carcinoma metastasize to the brain more commonly than squamous cell carcinomas). Metastases from unknown primary origin may constitute 5%-11% of cases. The literature data demonstrate that more than half of these cases have bronchial carcinoma as the primary tumor followed by breast and colon carcinomas and melanoma (8).

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SITES

Metastatic process may involve any part of the CNS including cerebral hemispheres (80%), cerebellum (10%-15%), brain stem (2%-3%), spinal cord, bones, dura mater, leptomeninges, pituitary and choroid plexus. In some cases metastases may be lodged in the pre-existing brain lesions (infarcts, hematomas, tumors). The great majority of CNS metastases usually reach the brain through blood circulation mostly via arterial circulation and less often via Batson venous plexus. Although blood-borne tumor emboli may lodge at any level of the central neuroaxis a few generalizations can be made regarding the topography of metastatic lesions. The great majority of metastatic deposits lie in the supratentorial or infratentorial brain compartments most likely owing to their volume and blood supply. These deposits are usually found in the arterial border zones (watershed zones) of the cerebral and cerebellar hemispheres. In the cerebrum, the most lesions settle within the frontoparietal cerebral tissue, in the tributary zone of the middle cerebral artery. The origin of cerebral metastases most frequently are lung (50%) and breast carcinomas (15%), melanoma (10%) and tumors of unknown primary site (2).

For reasons that are not clear, colorectal, uterine and renal carcinomas are over presented among cancers seeding the cerebellum. Dural metastases usually derive from prostate and breast carcinomas (9,10). The origin of spinal epidural metastases most commonly are from the breast (22%), lung (15%) and prostate (10%). Intramedullary spinal cord metastases are rather rare, but up to 40%-50% of them originate from lung carcinoma (3,11).

Diffuse infiltration of leptomeninges from solid tumors (leptomeningeal metastases or meningeal carcinomatosis) is frequently associated with breast, lung and gastro-intestinal carcinomas (12).

MACROSCOPY

Metastatic brain tumors usually are well circumscribed masses that displace rather than infiltrate the reactive adjacent brain parenchyma (Figure 1A). Superficial tumors involving the grey-white junction may invade the leptomeninges and show high incidence of seizures. The subependymal tumor deposits usually penetrate into ventricles. Metastases vary in size, from microscopic lesions to large masses up to several centimeters in diameter. Leaky tumor vessels result in an extensive edema which may be in disproportion with the relatively small size of the tumor nodule. Cystic lesions sometimes occur, particularly with the lung and breast carcinomas. Large tumors frequently undergo partial necrosis with a rim of viable tissue at the periphery (13).

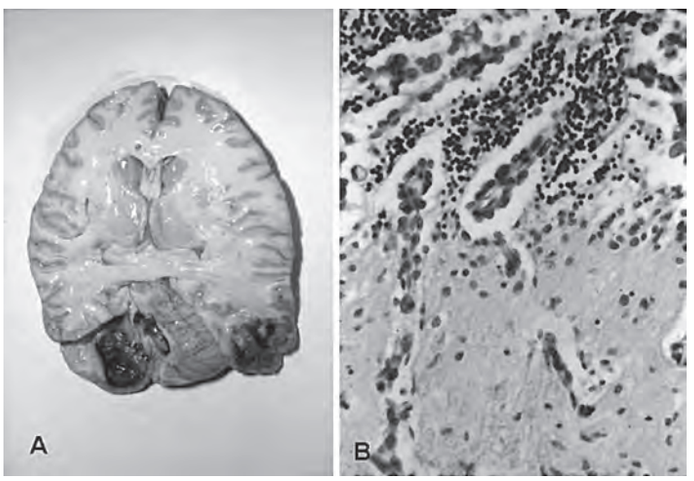

Figure 1. Metastatic lung adenocarcinoma. (A) Grossly, relatively well demarcated metastatic nodules in the occipital lobe and cerebellum, (B) microscopically show microinvasion of surrounding brain parenchyma

On cut surface, metastases are usually soft and pinkish grey. Zones of necrosis are softer with yellowish discoloration. Necrosis alone or with cyst formation is frequent. Some metastases, like melanoma, choriocarcinoma, lung and renal carcinomas have tendency to be hemorrhagic and may be presented as intracranial hemorrhages (14).

Metastases may be single or multiple. In general, 60%-80% of patients dying of cancer have multiple brain metastases at autopsy. The relative frequency of single or multiple metastases varies with type of primary tumor. As a rule, these tumors that frequently invade the CNS (e.g. melanoma and lung carcinoma) tend to produce multiple metastases, whereas cancers that only occasionally involve the brain (e.g. gastro-intestinal adenocarcinomas) are often presented by solitary deposits (2).

MICROSCOPY

Histopathologically, CNS metastases tend to be similar to the primary neoplasms. However, their degree of dedifferentiation may be more pronounced than in primary tumor as well as their proliferative activity. Therefore the primary site of metastatic tumor may be difficult to determine based solely on histopathology and owing to this the use of immunohistochemistry is necessary for establishing the diagnosis. When metastatic lesion is composed of small cells it may resemble primary brain tumor (glioblastoma) or metastatic neoplasms (e.g. malignant lymphoma, anaplastic carcinoma, melanoma and Ewing sarcoma). In such cases we are obligated to applicate the panel of markers for tumor immunophenotyping. Usually we use the following antibodies: glial fibrillary acidic protein (GFAP) for glial neoplasms, leukocyte common antigen (LCA) for lymphoma, cytokeratins (CK) for metastatic carcinomas, HMB-45 for melanoma and CD99 for Ewing sarcoma. Although the majority of metastatic lesions appear clearly demarcated from the surrounding brain tissue on gross examination, microinvasion of tumor cells is invariably present (Figure 1B). This finding is particularly noticeable in metastases of small-cell lung carcinoma and melanoma. Brain metastases may elicit a number of reactions in the surrounding parenchyma e.g. reactive astrocytosis, microglial activation and neovascularization, even with formations of glomeruloid structures which usually are not of so extend as in glioblastoma. The mechanism of neovascularisation is similar both in metastasis and glioblastoma and includes involvement of several growth factors, particularly VEGF (15). The neovascular network appears to be important not only in the development and maintenance of the metastatic lesion but also is a major contributing factor for vasogenic cerebral edema that accompanies brain metastases (16).

METASTASES OF UNKNOWN PRIMARY ORIGIN

As it was pointed out the metastases of unknown primary origin may constitute 5%-11% of cases (17). Even at autopsy the primary site may remain unknown. Because of that imunohistochemical diagnosis of such cases is necessary. In the present time there are a number of primary antibodies which may help in the immunophenotypic diagnosis of the majority of neoplasms.

The literature data concerning the diagnosis of metastatic origin are numerous (18-20). The panel of immunohistochemical markers are now available for identification the different primary sites including the most common sources of brain metastasis e.g. lung, breast, colorectal and renal carcinomas and melanoma (21). For metastatic lung adenocarcinoma the characteristic immunohistochemical profile are positivity of cytokeratin 7 (CK7) and thyroid transcription factor -1 (TTF-1), while CK20 is negative (22-25). Metastatic small-cell lung carcinomas are positive for low molecular weight keratins (CAM5.2), synaptophysin, neuron-specific enolase (NSE) and cacinoembryonic antigen (CEA); most of them show immunopositivity for TTF-1. Metastatic neuroendocrine lung neoplasms are positive for synaptophysin, chromogranine and NSE. Metastatic colorectal adenocarcinomas are CK20 positive and CK7 negative (26). Metastatic breast carcinoma are CK7 and CA 15-3 positive, estrogen/progesterone receptor positive or negative and TTF-1 negative (27). Metastatic renal cell carcinomas are positive for low molecular weight keratin (CAM5.2), keratin AE1/AE3, epithelial membrane antigen (EMA) and vimentin; immunoreactions for CK7, CK20, high molecular weight keratin and S-100 protein are negative. Metastatic melanomas are positive for S-100 protein and HMB-45 and negative for CK and EMA.

Finally, it is important to point out that successful immunohistochemical diagnosis needs well trained technicians, the sophisticated laboratory equipment and adequate financial support owing to the high prices of primary antibodies.

MOLECULAR GENETICS

The cases of colonic carcinoma expressing or overexpressing CD44R1 and breast carcinoma expressing c-erbB2 indicate the increased metastatic potential (28). In some tumors, decrease or loss of specific gene expression is associated with tumor progression (DCC in endometrial carcinoma, KAI-1 in prostate, lung, breast, bladder, pancreatic and hepatocellular carcinoma, and BA/1 in colon carcinoma (29-31). However, the investigation of genomic control in CNS metastases is in the early stage of investigation and only limited in formations are available (32).

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Cerebrospinal fluid cytology in metastatic disease of central nervous system – possibilities and dilemmas

KEYWORDS: Cerebrospinal Fluid; Cytodiagnosis; Central Nervous System Neoplasms; Meningeal Neoplasms; Neoplasm Metastasis; Immunohistochemistry

INTRODUCTION

It is well known that examination of cytological specimens obtained from cerebrospinal fluid (CSF) may be useful in the diagnosis of a variety of central nervous system (CNS) diseases, such as infectious, inflammatory or a neoplastic processes (1,2).
The primary diagnostic role for cytological examination of CSF is to detect malignant cells of clinically suspected tumor, as well as to follow up a treatment response of previously determined malignancy (3).
Leptomeningeal metastases (LM) are common problem in neuro-oncology, occurring in about 5% of patients with disseminated cancer (4). The incidence of LM increases with increased the life-span of patient who has the primary cancer. LM may be present as focal lesion or as diffuse infiltration of the subarachnoid space (leptomeningeal carcinomatosis) without apparent lesions in the brain or spinal cord parenchyma (5).
In most cases of LM in adults, the primary malignancy has already been diagnosed elsewhere, and CSF positive cytology simply confirms metastasis. In general, the same tumor types that produce solid brain metastases are also the leading causes of LM (6,7). Subarachnoid space is most receptive to the adenocarcinoma particularly those of the breast, lung and stomach (6,7). Carcinoma of other organs such as pancreas, female genital tract, bladder and prostate rarely has been detected in CSF (4,5,8). Metastasis of malignant melanoma and hematopoietic neoplasm are common (5,6). In rare occasions LM may be a first sign of occult primary tumor (9). In these cases, analysis of CSF cytology by immunocytochemistry may suggest possible primary site of tumor (10,11).
The prognosis of patients with LM is poor and patient survival is usually less than 6 months. Early diagnosis may improve the clinical response to radio- and chemotherapy, and may lead to more effective palliation and prolonged survival (4).

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GENERAL ASPECTS AND PITFALLS

A definitive diagnosis of LM requires cytological detection of malignant cells in the CSF. In most cases, malignant cells are easily recognized owing to their strikingly different morphology than the normal cells of CSF. In less number of CSF samples malignant cells are numerous. Unfortunately, CSF samples often contain very few morphologically identifiable malignant cells (3-5). Beside that, negative cytologic findings do not rule out the malignancy. In patients with known primary tumor it is sufficient to remark positive finding of tumor cells. In unknown primary tumor, nature and origin of tumor cells may be defined by immunocytological techniques.
Reported detection rates for malignant cells in CSF vary greatly in the literature, from 20.9%-83.3% (12). It seems that CSF cytology results are dependent on the type of tumor and a whole series of other factors, such as quantity of CSF sample, the location of the puncture, applied preparation methods and rapidity with which the preparation of the CSF specimens was made.
Some types of tumors, such as leukemia, usually show diffuse infiltration of subarachnoid space, opposite to metastasis of different solid tumors. There is relationship between the incidence of positive cytology and the extent of leptomeningal involvement by tumor. It is showed that cytological findings are more likely to be positive in patients with extensive, diffuse involvement of leptomeninges, than in patients with focal lesions (2,12).
Up to 90% of samples have too small of volume (<10mL), and more than 25% are processed to slowly (13). To prevent the deterioration of cells, collected fresh CSF sample has to be delivered to the laboratory as soon as possible (3,11). If the specimen cannot be prepared immediately, it should be refrigerated at 4∞C. Most laboratories now use a cytospin apparatus which is efficient in terms of cell yield. Cytospin preparations are air dried, fixed in methanol and stained by routine stains such as Papanicolaou, Gimsa and hematoxylin and eosin (3,11).
Most CSF specimens are obtained from the lumbar subarachnoid space via lumbar puncture (LP). Rarely, CSF is aspirated from other sites, including, the cysterna magna (14), ventricles (15) and shunts (16). Such specimens, particularly those from the cysterna magna region, have been reported to contain more malignant cells than are lumbar specimens. However, if clinical or imaging studies indicate that disease is present only at one site of leptomeninges, then CSF from that site is more likely to be positive than is CSF obtained from the more distant site (4,12).
Investigations have shown that sensitivity of a single cytologic CSF examination is about 50%. Second CSF sample from repeated LP increase the number of positive evaluations by 30% (10,12). However, no significant improvement in accuracy was found with additional samples (4).
Finally, for successful CSF cytology analysis, observer (pathologist) has an important role. First of all, pathologist has to know all relevant clinical data and then, must be familiar with: a) the normal cell constituents; b) reactive cellular processes in the CSF; c) nonneoplastic cell types that are sometimes present in CSF; and d) presentation of a spectrum of neoplastic cell types that may be present in CSF (5,17,18). Also, observer has to know how to minimize false negative results (13). Glantz et al. found that false-negative results could be minimized by withdrawing at least 10 ml of CSF for cytology, obtain CSF near the site of disease, delivering the CSF for immediate processing and performing another lumbar puncture. Pedersen et al. showed that in simple blind tests of slides (where the observer does not know the patients data), the percentage of positive results was considerably lower. The intraobserver and interobserver disagreement was 2% and 3%, respectively.
Morphologically atypical or obviously malignant cells can be present on slides either single or in small groups. At least 60% of those patients with a suspicious or atypical CSF cytology did in fact have meningeal carcinomatosis. Non specific inflammatory response often accompanies meningeal implants of metastases and seeding by primary CNS neoplasm. The most common cause of false-positive diagnoses is over diagnosis of malignant lymphoma

or leukemia, particularly in patients with viral meningitis, and in LP specimen contaminated with blood (3,4,6).
In the follow up of treatment response of leptomeningeal metastases, CSF cytology is only moderately sensitive because of a decrease in cell number and changes in cell morphology. Because of that some new approaches such as biochemical markers (20), and molecular cytogenetics take an important role (21).

MOST FREQUENT METASTATIC TUMORS AND DILEMMAS

Carcinoma of the lung

All histologic subtype can be seen in CSF (5,19,22). Adenocarcinomas are most common (6). Tumor cells may be large, with abundant cytoplasm and an eccentrically placed nucleus. The cells are singly dispersed or arranged in small groups (3). When the signet ring cell differentiation is seen it may be diagnostic dilemma to gastric adenocarcinoma. Small cell carcinomas when present as isolated cells may be easily mistaken for lymphocytes. Single cell necrosis, nuclear molding and frequent mitosis are characteristic features. Detection of squamous-cell carcinoma in CSF is infrequent.
Lung is the most common occult primary site, followed by gastric cancer and melanoma.
Immunocytochemical analysis, using panel of antibodies (CK7, TTF-1, CK20, HMB-45) can help in detection of primary site of tumor.

Carcinoma of the breast

Ductal carcinoma is the most frequent. It is characterized by large atypical cells with round irregular nuclei, prominent nucleoli and often scant cytoplasm. The cells may be single or grouped in clasters, linear rows or sometimes in glandular arrays. Cells of lobular carcinomas are smaller and frequently arranged as isolated cells (3,24). Similar to lung carcinoma, signet ring cell differentiation may be present in both types of breast carcinoma. It must be noted, that isolated signet-ring cells are not adequate evidence for diagnosing a carcinoma since such formation are often found also with activated monocytoid cells. Immunofenotyping of these cells is very useful (CK7 and CA15-3 for breast carcinoma; CD68 for macrophage).

Malignant melanoma

It metastasizes to CNS and frequently presents in the CSF. Melanoma cells are large, with round or irregular nuclei and prominent nucleoli. Cytoplasm may be scant or abundant and may contain a finely granulated brown to black pigment. Tumor cells are isolated or only loosely aggregated. When the cells are without pigment, distinction from carcinoma and glioma cells may be impossible without immunostaining (3,4,23). HMB-45 and S-100 are positive, whereas stains for cytokeratin, EMA and GFAP are negative.

Leukemia and lymphoma

Owing to successful cytostatic therapy, life span of leukemic patients is extended but there is higher the chance of the CNS involvement (2,4,5). Subarachnoid space is the most commonly infiltrated by different type of leukemia and lymphoma. The cytological diagnosis generally produces no difficulties when leukemic disease has already been established (3). However, sometimes these disorders such as acute nonlymphocytic leukemia (monocytic and myelomonocytic subtypes) and lage cell lymphoma are present initially with meningeal symptoms, and with large numbers of malignant mononuclear cells in CSF (5). In the absence of systemic involvement, the initial diagnosis of leukemia or lymphoma should be made with caution, because significant atypia can be seen in lymphoid cells in patients with infectious conditions, particulary of viral and fungal etiology (5,25,26). If the process is not obvious on a morphologic basis, immunophenotyping is helpful. Prophylactic and intrathecal chemotherapy, with neuraxis radiation reduced the incidence of CSF involvement in childhood ALL from 70%-80% to less than 15% of cases. (5). Periodic monitoring of CSF for the presence of blasts is essential (27).
The low grade lymphomas, such as small cleaved and noncleaved types, as well as chronic lymphocytic leukemia and Hodgkin's disease are uncommon in CSF, and the majority of patients with these disease prove to have CNS infections rather than neoplastic infiltrates (3,4,5)

CONCLUSION

The gold standard for diagnosing leptomeningeal metastases is still cytologic confirmation of malignant cells in the CSF.
Although, CSF cytology has limitations and there are many cases in which it is hard to achieve a firm diagnosis, the application of immunocytochemical and especially molecular biologic techniques will advance the diagnostic capabilities of CSF cytology and probably increase its important.

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Radiotherapy of metastatic CNS disease

KEYWORDS: Central Nervous System Neoplasms; Neoplasm Metastasis; Radiotherapy

Radiotherapy of the metastatic CNS disease is a palliative procedure which aim is to achieve maximum benefit with minimum treatment – elimination or prevention of symptoms, improvement of life quality and, if possible, prolonged survival. Generally, its emergence application, within the shortest possible time period, which includes hypofraction radiotherapy regime, is warranted.

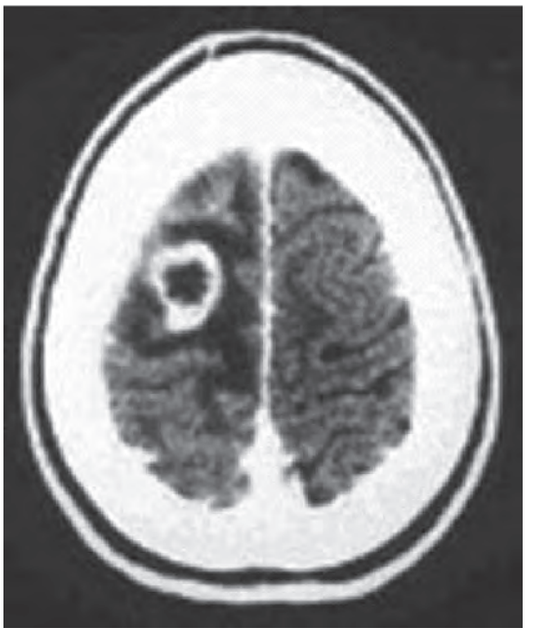
In the most favorable group from the prognostic point of view, in which either solitary metastasis or up to 3 metastases are evidenced upon MRI the initial approach includes surgical removal of the change, while in case that surgery is not possible regardless of the reason, radiosurgery is applied – focused radiation of the region affected with the metastases with high radiation doses (up to 20 Gy) with sparing of the surrounding unaffected tissue (Figure 1).

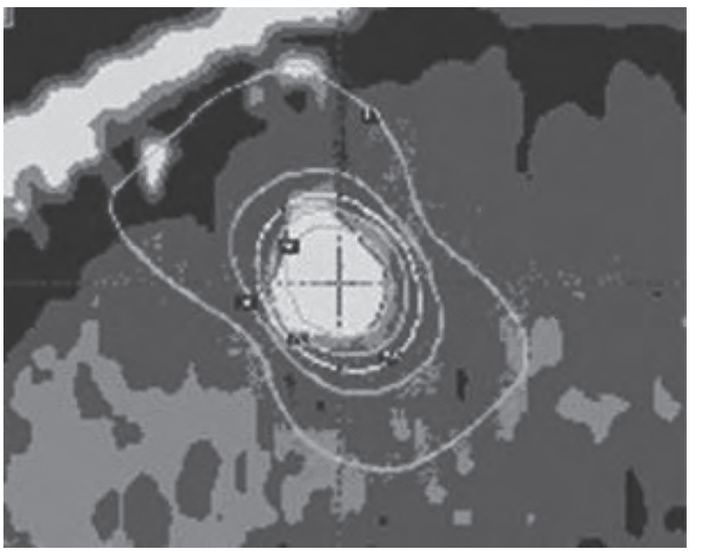
To the patients with multiple brain metastases (more than 3), palliative radiation therapy of the brain is applied, based on the specific radiation regimes, which depends on the general health status of the patient and number and size of the metastatic changes. The most frequently applied are doses of 30 Gy in 10 sessions or 20 Gy in 5 sessions, In patients with short expected survival, the radiotherapy is carried out according to the concentrated regime with TD 12 Gy in 2 sessions, or less frequently with 18 Gy in 3 sessions (Figure 2).

Leptomeningeal metastases developing in cases of breast carcinoma, leukemia and malignant melanoma are rare and least favorable from the prognostic point of view. They necessitate application of the craniospinal axis radiation therapy.

Prophylactic brain radiation is a particular type of the radiotherapy aimed at treatment of the metastatic disease in the malignancies having high brain metastasizing affinity, such as small cell lung carcinoma, leukemia and lymphoma. As for the hematological diseases, the dose ranges between 12-18 Gy while in the small cell lung carcinoma it ranges between 30 and 36 Gy. It has been evidenced that preventive CNS treatment undoubtedly delays onset of brain metastases, however, it does not compromise therapeutic radiation dose in subsequently developing metastases.

Survival of patients subjected to the treatment is 4 months at the average, while approximately 8% survive for 2 years. Radiotherapy combined with surgery plays the major role in treatment of these patients, since in spite of the short survival period, the effect of the radiotherapy is related to symptomatic improvement.





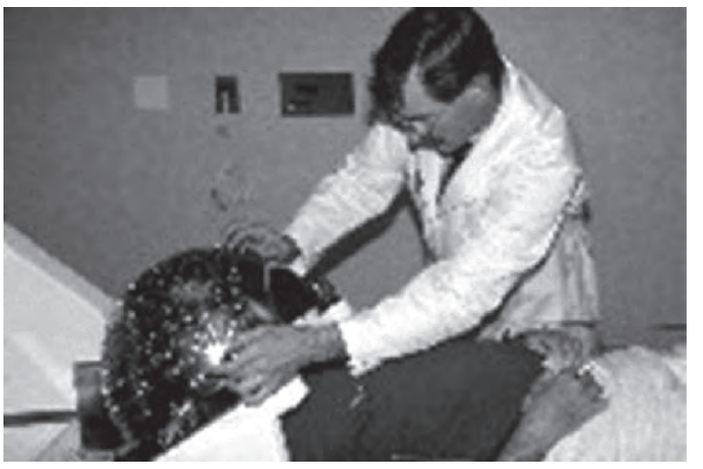


Figure 1. Radiosurgery for solitary brain metastasis

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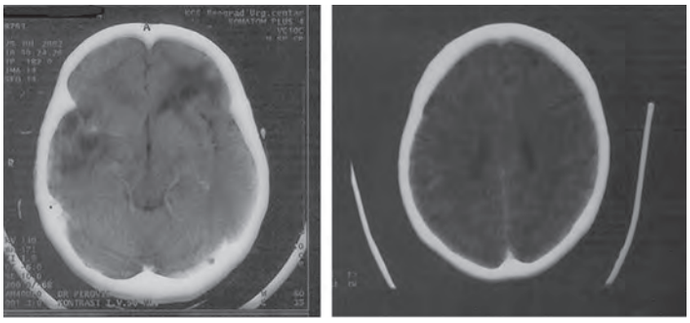

Figure 2. Total regression metastases in CNS after radiotherapy

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Radiosurgery for brain metastases

KEYWORDS: Brain Neoplasms; Neoplasm Metastasis; Radiosurgery; Stereotaxic Techniques

INTRODUCTION

Brain metastasis is the most common intracranial tumor in adults. The autopsy reports indicate 25% to 50% incidence of brain metastases in patients who die of cancer (1). Brain metastases represent a major source of morbidity and mortality in cancer patients. Patients with lung cancer, breast carcinoma, melanoma, renal cell and colorectal cancer, have a greater propensity for the same (2,3). Approximately 40% of these patients have a solitary or single metastasis and many of them harbor two or more metastases (2). Most patients develop involvement of the brain late during the course of metastatic cancer. Left untreated, the median survival is one month. Treated with steroids alone, the median survival rises to 2 months (4). Important prognostic factors for better survival (more than 7 months) are: good performance status, absence of extra cranial metastases, controlled primary tumor and age less than 65 years (4,5).
Current treatment strategies aimed at palliation of symptoms and preservation of neurological function, include corticosteroids, whole brain radiation therapy (WBRT), surgery, chemotherapy, radiation sensitizers and radiosurgery (RS) (6). Symptomatic management can result in a significant improvement in quality of life. Vasogenic edema secondary to metastasis typically responds to treatment with corticosteroids (6). Craniotomy with removal of accessible metastasis and whole brain fractionated irradiation therapy (WBRT) has been used as established treatments (7-9). The goals of surgery are to obtain immediate symptom relief, gain local control, histological confirmation, relieve recurrent persistent symptoms after non-surgical treatment and placement delivery devices (Ommaya) for chemotherapeutic or isotope (10). Surgery is an important modality for patients with single brain metastasis, when favorable prognostic factors and systemic disease control are present (11).
Radiosurgery or stereotactic radiosurgery (SRS) has been developed in order to avoid open cranial surgery and its complications (12). Recent developments in computer technology for dose planning, as well as refinements in radiation delivery systems have led to a veritable interest in radiosurgical treatment, for selected patients suffering from a variety of neurosurgical disorders (AVM, acoustic neurinomas, functional disorders, metastatic tumors) (12,13).

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DIAGNOSIS

CT or MRI establishes the diagnosis of brain metastases. On CT or MRI, most brain metastases are enhancing lesions surrounded by edema, which extends into the white matter. The radiographic appearance of brain metastases is nonspecific and may mimic non-tumor processes (13). MRI is the superior test and should be performed whenever feasible in any patient being evaluated for metastatic brain disease. A high-quality, contrast-enhanced MR scan should be obtained to define the number of metastatic nodules and to look for evidence of leptomeningeal disease (14).

Principles of radiosurgery (RS)

RS is the non-invasive delivery of a precise single dose of high-energy radiation to a tumor or lesion. RS uses radiation to shrink or control the growth of a tumor by killing tumor cells and interfering within their ability to growth (15). All radiosurgical systems achieve this goal by the combination of the three elements: 1. Stereotactic localization of the intracranial lesion; 2. Precise collimation of the radiation beams so that it tightly fits the dimensions of the target and 3. Administration of the total dose through multiple beams that come from different points in space and intersect at only one point-the intracranial target (16).
Three facilities exist: Gamma knife, LINAC and proton beam[1]. Photons are the most commonly used particles in the radiotherapy of the brain tumors. Examples for non-photon irradiation modalities (available in experimental facilities are neutrons, protons, helium ions, pions and heavy ions (carbon, argon, neon). The hallmark of stereotactic radiosurgery SRS is the rapid dose fall off at the target edges, permitting a clinically significant dose to be given to the target while a clinically insignificant dose is delivered to the surrounding normal brain (17). The treatment dose to the tumor margin typically is between 15 to 20 Gy and is based on tumor size, location, history of prior radiotherapy and dose overlap from the treatment of other metastases. Although it is called surgery, SRS is actually no incision and it is often performed on an outpatient basis. In comparison to craniotomy, SRS has several advantages: 1) brief or no hospitalization; 2) avoids risk of general anesthesia, hemorrhage, infection and tumor seeding, and 3) lower costs (16). Weighing the options, there is an ongoing debate about whether surgery or radiosurgery is better option for treating brain metastasis and under what circumstances.
Metastases are considered ideal targets for SRS, since they are radiographically distinct and often spherical, usually small (<3 cm), displaced of normal brain tissue, and minimally invasive. SRS is the option of choice for deep seated lesions, and important treatment tool in both primary and secondary brain metastases (17).
SRS is considered by many investigators to be effective and equivalent to surgical resection of solitary brain metastasis with local control of tumor rates ranging from 70%-94%. Median survivals of patients treated by SRS, have ranged from 6 months to 1 year (18,19).

History

The first case of radiosurgery was reported by Leksell in 1949 using multiple small and fixed semicircular radiation beams at different angles to treat an intracranial target. The first attempts to supplant instruments with stereotaxically directed narrow beams of ionizing radiation were made in 1951 (20). Initially, relatively low energy x-rays were used, but even then use of high energy gamma rays appeared an attractive possibility. Extensive studies in goats, using the proton beam of the 185 MeV synchrocyclotron in Uppsala, and clinical tests in a small group of patients with Parkinsonism gave valuable information concerning the anatomy of the radio lesions and the doses of radiation required (21,22). This technique became more reliable and

[1] Proton radiosurgery offer optimal physical characteristics for stereotactic applications, but this technique is only available in very few centers (USA).

reproducible when the Gamma Knife was introduced in 1955 (The first operation on man) which uses Cobalt-60 to produce multiple, intersecting static beams (23). The physical aspects were thoroughly investigated by Linden (1957), and Larsson and Linden 1962 and the unit constructed by AB Motala Verkstad, Motala.
Clinical studies using modified linear accelerator began in early 1980s. Colombo and Sturm reported, in 1985 and 1987, experience on the radiosurgical treatment (LINAC) in patients with brain metastases with good results (24,25).

GAMMA KNIFE

The present 60 Gamma Unit was specially designed to be included in Leksell stereotaxic system. The Gamma Knife contains 201 small cobalt sources of gamma rays arrayed in a hemisphere within a thickly shielded structure (Figure 1).

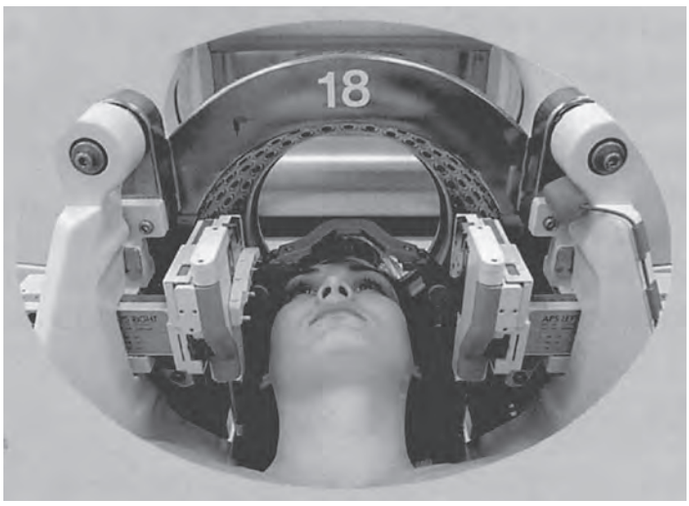

Figure 1. Gamma Knife

A primary collimator aims the radiation emitted by these sources to a common focal point. A second collimator, which fits within the primary collimator, allows the beam focus size to be adjusted from 4 to 18 mm in size. The computer software reduces the treatment plan to a list of simple instructions to guide the gamma rays to the target. Before the Gamma Knife radiosurgery, the Leksell Stereotactic Coordinate Frame is fixed to the patient's head. The frame provides the basis for target coordinate determination and is used to immobilize and position the patient's skull within the collimator helmet. The Gamma Plan permits the user to calculate and adjustment of shot positions. The gamma angle can be changed to avoid the collision between patients head and helmet. The quality of treatment is a result of achieving the suitably and precisely target position (26).

Practice with Gamma Knife

A Leksell model G stereotactic head frame was applied to the head of the patient under sedation and local anesthesia for the purpose of target localization. Target localization was done on 1-mm thick, gadolinium-enhanced, high resolution, axial MR images obtained with spoiled gradient-recalled acquisition in steady-state sequence using a 1.5-Tesla Sigma MRI. The images were then transferred to the gamma knife computer through Ethernet. Radiosurgery-dose planning was performed using the Leksell Gamma Plan software version 5.3 by a team comprised of a neurosurgeon, radiation oncologist, and the medical physicist. Tumor volume ranged from 0.5 to 33 cm^3. Mean margin dose prescription to the tumor was 15 Gy. A 50% isodose line was used in all cases to conform the dose to the tumor margins. Then radiosurgery was administered (27) (Figures 1, 2).

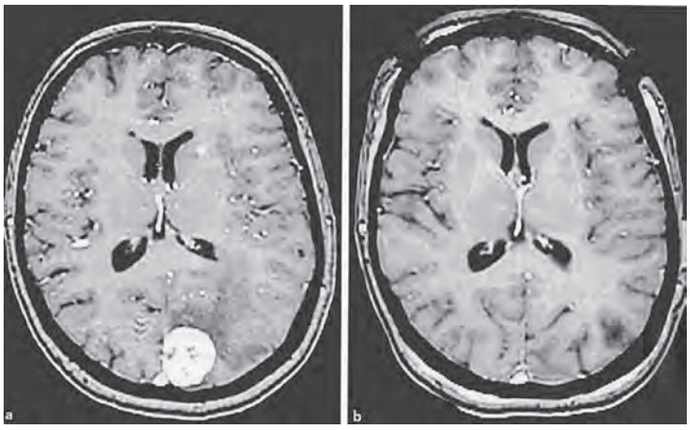

Figure 2. Preoperative (a) and postoperative (b) contrast axial MRI scans of a 41-year-old female with multiple brain metastases from breast carcinoma, treated with gamma knife radiosurgery (27)

LINAC (Linear accelerator)

All linear accelerator radiosurgical systems rely upon the following basic paradigm: A collimated x-ray beam is focused stereotactically to identified intracranial target. The gentry of the linear accelerator rotates over the patient, producing arc of radiation focused on the target. The patient couch is then rotated in the horizontal plane and another arc is performed. In this manner, multiple, noncoplanar, intersecting arcs of radiation are produced. In the fashion exactly analogous to the multiple intersecting cobalt beams in the gamma knife, the intersecting arcs produce a high target dose, with minimal radiation to the surrounding brain. New Technology for radiation delivery called "Conformal therapy" for linear accelerator radiosurgical systems, relies upon dynamically shaping the treatment beam to fit the "beam's eye view" of the lesion (28).

Intracavitary / Interstitial brain irradiation

Cosgrove reported the use of a novel SRS device GliaSite® radiotherapeutic system (RTS) for interstitial irradiation of malignant brain tumors. It is a single-applicator system that is used to deliver a conformal dose of 60 Gy of radiation to a depth 10 mm beyond the resection cavity at risk for tumor recurrence.
Fourteen patients with cerebral lesions less than 3.5 cm in the greatest diameter were treated with 12.5 Gy of radiation. Evaluation of device GliaSite® radiotherapeutic System for the treatment of resected solitary brain metastases is ongoing in a multicenter prospective phase II study (FDA approval) (29).

Radiosurgery plus / versus whole brain radiation?

For patients with a single lesion, SRS+WBRT improve survival compared to WBRT alone (30-32) (Figure 3).

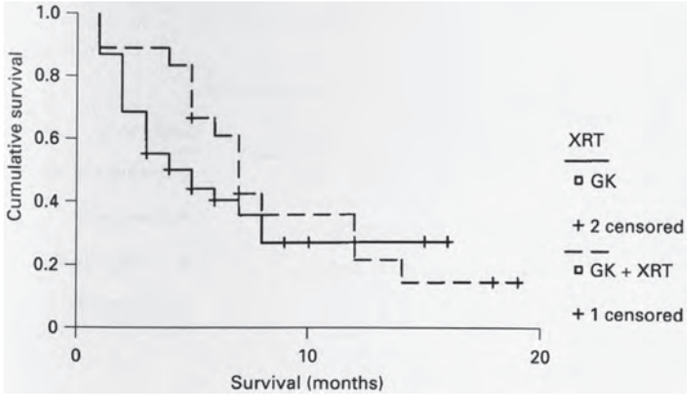

Figure 3. Survival as a function of additional XRT (GK = Gamma knife)

In selected patients treated with radiosurgery alone for newly diagnosed brain metastases, overall survival is not altered (30). Clinical trials are ongoing to determine if WBRT can be safely omitted in patients with single brain metastases (33). In the control of disease, the effect of SRS combined with WBRT in patients harboring two to four metastases has been shown to be superior to WBRT alone (33). However, local and distant brain control is significantly poorer with omission of up front whole-brain radiotherapy (34). SRS is an appealing technique for the initial management of small deep-seated lesions as a boost to whole brain radiotherapy (35).

There is a small risk of toxicity associated with radiosurgery boost as compared with whole-brain radiotherapy alone. It is still not known whether neurocognition or quality of life outcomes are different between initial radiosurgery alone vs. whole-brain radiotherapy (with or without radiosurgery boost) (36).

There is insufficient evidence as to the clinical benefit/risks radiosurgery used in the setting of recurrent or progressive brain metastases, although radiographic responses are well-documented. Stereotactic radiosurgery is considered as an effective and relatively safe treatment for recurrent solitary metastases (37,38).

CONCLUSION

The goal of multimodality treatment for brain metastases is to palliate local symptoms and prevent consequences of neurological involvement. Although the average prognosis for an individual with brain metastases is poor, selected patients will benefit significantly from combined treatment modalities. Stereotactic radiosurgery is a safe and effective treatment option for patients with cerebral metastases. It provides survival benefits and improves quality of life by achieving excellent control of the brain disease, irrespective of patient's age or number of brain tumors.

Ongoing research is aimed at refining criteria to select which patients with brain metastases should undergo surgery or SRS, and how these focal therapies should be optimally integrated with whole-brain radiotherapy (39).

All radiosurgical patients must be followed by neurosurgeons, radiation physicists and radiation therapists to optimize this technology. Neurosurgeons are responsible for verifying and adequacy of radiosurgical systems, selecting patients, treating them with a team approach that applies the latest available knowledge of neurosurgery and other relevant disciplines (28,40).

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Paraneoplastic syndromes

KEYWORDS: Paraneoplastic Syndromes; Paraneoplastic Syndromes, Nervous System

INTRODUCTION

Paraneoplastic syndromes are the group of disorders associated with cancer but without direct effect of the primary tumor mass or metastasis in the involved organ (1,2). Using above mentioned definition, any nervous system dysfunction caused by nonmetastatic effect of cancer can be called paraneoplastic neurological syndromes (PNS) (3), (Table1).

Table1. Nonmetastatic effects of cancer of nervous system

– **Metabolic disorders**
Organ failure
Endocrinopathies
Nutritional problems
Tumor secretion of ectopic substances
– **Vascular disorders**
Hypocoaguability (hemorrhage)
Hypercoagulability (infarction)
– **Infection**
Side effects of therapy
Surgery
Irradiation
Chemotherapy
– **"Remote effects"**
Brain and cranial nerves
Spinal cord and root ganglia
Peripheral nerves
Neuromuscular junction
Muscle

(Posner JB, Paraneoplastic Syndromes Involving the Nervous System. In: Aminoff MJ. Neurology and General Medicine. New York: Churchill Livingstone; 1995;401-421)

However, concerning the neurological point of view the term PNS can be defined as remote effects of cancer and they are not caused by tumor or metastasis, or infection, or ischemia, or metabolic disruption or by side effects of cancer therapy (3). PNS are seen in about 1% of patients with cancer (4). They are most commonly associated with small cell lung cancer (SCLC) and occur in about 3% of cases (5). Other tumors associated with PNS include breast and ovarian cancers and Hodgkin's disease (5). Classification of PNS is shown in the Table 2.

Table 2. Paraneoplastic neurological syndromes

Brain and cranial nerves
Subacute cerebellar degeneration
Limbic encephalitis
Brainstem encephalitis
Opsoclunus-myoclonus
Photoreceptor degeneration
Spinal cord and dorsal ganglia
Necrotizing myelopathy
Myelitis
Sensory neuronopathy
Peripheral nerve
Subacute or chronic sensorimotor peripheral neuropathy
Acute polyradiculoneuritis
Mononeuritis multiplex and vasculitis of peripheral nerves
Brachial neuritis
Subacute motor neuropathy
Peripheral neuropathy with islet cell tumors
Peripheral neuropathy with paraproteinemia
Neuromuscular junction and muscles
Lambert-Eaton myasthenic syndrome
Dermaotomyositis/Polymyositis
Acute necrotizing myopathy
Carcinoid myopathy
Neuromyotonia
Stiff man syndrome
Multiple levels of central and peripheral nervous system or unknown site
Encephalomyelitis/Subacute sensory neuronopathy
Neuromyopathy

(Modified from Posner JB, Paraneoplastic Syndromes Involving the Nervous System. In: Aminoff MJ. Neurology and General Medicine. New York: Churchill Livingstone; 1995;401-21)

Pathogenesis

Most of PNS, if not all, are believed to be autoimmune diseases in which antitumor immune response also attack neurons that express shared neuronal tumor antigens thus causing neurological dysfunction (6). Most of these onconeural antigens are located in the cytoplasm-nuclear compartment of the cell, whereas others are located at the membrane and act either as receptors or as ion channels (7). Affected patients often have one or more circulating antineuronal antibodies, which serve as a diagnostic marker for the paraneoplastic condition, and in some cases are the direct mediators of neuronal injury (7). The exact immunopathogenesis and relative contributions of humoral or cellular immune effectors for most PNS are not well understood (3,7,8).

Diagnosis

In most patients, PNS develop before the cancer becomes clinically overt. PNS usually affected patients in their sixth decade (4). The cancer is usually found within several months to a year after the neurological symptoms begin, but occasionally the cancer may elude detection for 2-4 or even more years or has been found only at autopsy (3). Most PNS are subacute in onset, progress over weeks and months, and then some of them stabilize (3). Although the majority of patients with PNS have clinical evidence of diffuse involvement of neuraxis, it is very important to focus to the clinical syndrome that predominantly affect one specific portion of the nervous

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system. Depending on the part of the nervous system affected, the workup may include computed tomography (CT) or magnetic resonance imaging (MRI) in order to exclude parenchymal or epidural metastasis, CSF examinations exclude leptomeningeal metastasis, measuring metabolic, endocrine substances and coagulation factors and/or electrophysiological examinations (3). In patients without known cancer, if other causes of nervous dysfunction have been excluded, evaluation for systemic cancer must be carefully performed. To search for the underlying cancer in patients with PNS, fluorodeoxyglucose (FDG) positron emission tomography (PET) is widely recommended (9).

It is now accepted that the best way of diagnosing PNS is to identify one of the well characterized antineural antibodies in patient's serum (10). It is well-known that these antibodies are associated with restricted range of cancer, and they permit the search of underlying tumor at a stage which is frequently not clinically overt. Although there are now many different paraneoplastic antibodies that have been described, there are still relatively few that are reliably measured routinely (4). In addition, antineural antibodies are positive in about two-third of PNS patients. Currently, the antibodies include those to Hu (ANNA1), P/Q type voltage gated calcium channels (VGCC), Yo (ANNA2), Ri CRMP5 (CV2) Ma2, amphiphysin (8). With the exception for the Lambert Eaton myasthenic syndrome, the etiopathogenic significance of most of these autoantibodies is not clear (3). However, their presence helps confirm the clinical diagnosis of PNS and further focuses on search for underlying malignancy.

Treatment

Rapid detection and immediate treatment of underlying tumor appears to offer the best chance of stabilizing the patient and prevent further neurological deterioration (4). Most of the additional therapies tried have been forms of immunosuppression, particularly for these syndromes that are associated with autoantibodies (5). However, with the exception of the LEMS in which plasmapheresis or intravenous immunoglobulins is clearly effective, in most patients with other forms of PNS such treatment has not been consistently beneficial (11,12).

SPECIFIC PARANEOPLASTIC NERVOUS SYSTEM SYNDROMES

Only a few of the most common syndromes are considered in this review.

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) is a one of most frequent PNS (5). It can be associated with any cancer, but most common are lung cancer, especially SCLC, ovarian or uterine cancer and lymphomas, particularly Hodgkin's disease (2,3,13,14). Typically, the disorder begins with incoordination in walking and progresses within a few months to gait ataxia, incoordination in the arms, legs and trunk; dysarthria, nystagmus and vertigo (14). In around 50 percent of patients, other neurological abnormalities including sensoneural hearing loss, extrapyramidal signs, peripheral neuropathy, mental status abnormalities may be found. Microscopically, the hallmark of PCD is severe or complete loss of Purkinje cells of the cerebellar cortex. Early in the course of the disease, CT scan and MRI do not reveal abnormality. Within a few months to a few years, diffuse cerebellar atrophy appears (2). In most patients who studied early the CSF contains an increased number of lymphocytes elevated protein and IgG concentrations as well as oligoclonal bands. Several paraneoplastic antibodies have been identified in patients with paraneoplastic cerebellar degeneration (5). Their association with particular cancer may help identify an occult lesion. Anti Hu antibodies as well as VGCC may be common in pure PCD associated with SCLC (8). Anti-Yo antibodies are directed against Purkinje cell antigens and occur in patients with cerebellar degeneration who have breast cancer or gynecologic tumors (15). Therapeutic options include tumor excision, chemotherapy and/or irradiation, and adjuvant therapy with glucocorticoids, immunoglobulins and plasmapheresis (5). Sometimes disorder may remit spontaneously or coincidentally with the treatment of the tumor (2).

Paraneoplastic encephalomyelitis / sensory neuronopathy

Paraneoplastic encephalomyelitis/ sensory neuronopathy (PEM/SN) is most frequent PNS, that is, is characterized by inflammatory infiltrates and neuronal death in several areas within the brain, brainstem, spinal cord dorsal root ganglia and nerve roots (2,3,16). PEM/SN is usually associated with SCLC although clinically and pathologically similar disorders have been described with the other tumors (16). The signs include dementia, cerebellar degeneration, brain stem dysfunction, myelopathy, sensory neuronopathy. PEM/SN is often associated with anti Hu antibodies. Over 85% of patients with high titer of anti Hu antibodies and PEM/SN harbor a lung cancer, usually SCLC (17).

Paraneoplastic limbic encephalitis

Paraneoplastic limbic encephalitis (PLE) is a rare neurological manifestation of malignancy. It is typically presented with short-term memory loss, seizures, or other limbic system abnormalities. The majority of PLE cases are associated with lung and testicular and ovarian cancer (18). It may occur as an isolated syndrome or in association with encephalomyelitis or sensory neuronopathy (2,3,5). The pathological changes are usually limited to limbic and insular cortex though deep gray and white matter structures may be involved. Extensive loss of neurons with reactive gliosis, lymphocytic cuffing and microglial proliferation typify this syndrome. MRI usually appears normal, although abnormalities in the medial temporal lobe(s) have been reported. Half of all patients with limbic encephalitis and SCLC have anti-Hu antibodies (5). No treatment has been consistently beneficial, although reports relate to spontaneous remissions or improvement to treatment of underlying tumor (18).

Paraneoplastic brainstem encephalitis

Paraneoplastic brainstem encephalitis, characterized by the subacute development of lower brainstem or basal ganglia signs, usually occurs as a part of more diffuse syndrome of encephalomyelitis, although it is sometimes presented as an isolated clinical syndrome. Any cranial nerve may be affected3. Movement disorders include chorea, dystonia or myoclonus.

Paraneoplastic opsoclonus-myoclonus

Opsoclonus-myoclonus syndrome is distinct neurological disorder characterized by opsoclonic eye movements, multifocal myoclonus and ataxia. Such syndrome is present in 2% of children with neuroblastoma (20).

Paraneoplastic opsoclonus-myoclonus with ataxia (POMA) is more common in patients over 40 years and it is usually associated with lung (especially SCLS), breast and ovarian cancer. The CSF has a mild pleocytosis and mildly elevated proteins. MRI is usually normal. The anti Ri antibodies are commonly found in patients with this syndrome associated with breast cancer (21). The results for treatment POMA are disappointing, although aggressive multimodality immunosuppressive treatments have been used.

Paraneoplastic myelitis

Paraneoplastic myelitis occurs rarely as an isolated syndrome but more commonly as a part of diffuse encephalomyelitis. It may be presented as non-necrotizing or necrotizing paraneoplastic myelitis (2). In the former pathologically, an intensive inflammatory reaction and loss of neurons in the anterior and posterior horns are seen with secondary nerve root degeneration and neurogenic muscular atrophy (3,6). Pathologically, in paraneoplastic necrotizing myelitis there is widespread spinal cord necrosis involving all components of the cord. Inflammatory lesions are not typical. Sometimes MRI show spinal cord swelling or even contrast enhancement. Paraneoplastic myelitis with SCLC is associated with anti-Hu antibodies (4). Treatment is usually unsuccessful.

Paraneoplastic neuropathy

Paraneoplastic neuropathy (PN) represents clinical and immunological heterogeneous conditions (5,22). Almost every clinical type of neuropathies has been described as a PN (22,23). Sometimes the tumor is discovered months or even years after the appearance of the neuropathy. The most

frequent is subacute sensory neuronopathy and then sensory-motor neuropathy and sensory neuropathy. Around 50%-60% of patients with PN have detectable antineural antibodies, such as anti Hu, anti CRMP5, ANNA3 (5,22). Subacute sensory neuronopathy is thought to be the most frequent presentation of the anti-Hu syndrome, but it seems that sensory-motor neuropathy is other common form in the anti-Hu neuropathy (23). Sensory or sensory-motor neuropathies with anti-CV2 antibodies are less frequent. The link between the cancer and the neuropathy is less clear in the other forms of neuropathies. The frequency of cancer in this group varies from 1 to 18 percent. These neuropathies include inflammatory demyelinating neuropathies, paraneoplastic vasculitis of peripheral nerve, lower motor neuron diseases, and autonomic neuropathies. Occasionally, the neuropathy improves with treatment of the tumor.

Subacute sensory neuronopathy

Subacute sensory neuronopathy (SSN) is characterized by subacute onset and progressive impairment of all sensory modalities and areflexia, associated with severe sensory ataxia (2,3). Cranial nerves may also be involved. Motor function is preserved. SCLC accounts more than 80 percent of tumors associated with SSN (5). The CSF is typically inflammatory. Relentless destruction of dorsal root ganglion cells by cytotoxic T cells leads to a poor prognosis About 50 percent of patients with this syndrome have pathological changes in other regions of CNS (3). In most patients treating the underlying tumor, plasmapheresis or immunosuppressive therapy do not alter the course of this neurological disease.

Paraneoplastic Lambert- Eaton myasthenic syndrome (LEMS)

It is acquired organ specific autoimmune presinaptic disorder of neuromuscular junction. The main clinical characteristics of the disease are proximal muscle weakness of the extremities, predominantly affecting legs, augmented strength with prolonged or repeated muscles activities, depressed tendon reflexes and autonomic phenomena (25). The association with small-lung carcinoma is present in 60% of LEMS. In paraneoplastic LEMS(P-LEMS) patients VGCCs of tumor cells provoke immune response with cross reaction towards nerve terminals resulting in neurological symptoms (26,27). The diagnosis can be confirmed by detecting the specific P/Q VGCC autoantibodies in radioimmunoprecipitation assay, and by electrophysiological finding, a reduced compound muscle action potential amplitude that increases by > 100% following high frequency stimulation. Specific carcinoma therapy in P-LEMS will often ameliorate neurological disorder (26,27). IV imunoglobulins or plasmapheresis confers short term benefit in patients with prominent progressive weakness (26,27).

Paraneoplastic dermatomyositis/polymyositis

Only minority of patients suffering from these diseases have underlying malignancy as their cause. Some investigators have concluded that the incidence of cancer is substantially higher in patients with these disorders, particularly in the older age group (2,3). Dermatomyositis is more frequently present as paraneoplastic than polymyositis. The clinical and laboratory findings in dermatomyositis/polymyositis with malignancy resemble to those in classic diseases. In some patients these disorders can improve coincidentally with treatment of the tumor.

Neuromyotonia

Neuromyotonia is rare but clinically significant disorder which is characterized by progressive aching and stiffness of muscles associated with spasms or severe rigidity that prevents muscle to be used. Electrophysiological studies indicate continuous muscle fiber activity. Patients with neuromyotonia may have autoantibodies to Shaker-type potassium channels (28). Such disorder can be associated with lung cell cancer and thymoma. Treatment of underlying tumor and plasmapheresis may be successful in combination with symptomatic treatment.

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Diagnosis and treatment of spinal cord metastases

KEYWORDS: Spinal Cord Neoplasms; Neoplasm Metastasis; Epidural Neoplasms; Meningeal Neoplasms; Diagnosis; Antineoplastic Agents; Radiotherapy

INTRODUCTION

The importance of metastatic disease of spinal cord, may be seen from the epidemiological findings that show 5 to 14% spinal cord metastasis in all patients treated from carcinomas (1). The fact that symptoms of metastatic spinal cord disease are very mild in the beginning, and that they precede 2 to 4 months to the definitive lesion of medulla, manifest the actuality to this problem. In this period of time, we should come to correct diagnosis and start with proper therapy, witch can prevent difficult and latter irreversible damage of the spinal cord. This can also lead to longer survival of the patients and better quality of their life. For these reasons, metastatic disease of spinal cord is an urgent medical problem in neurology, oncology and neurosurgery.
Spinal cord lesions from metastatic spreading of primary disease, can be, direct or indirect. Direct lesions are located in: (1) spinal cord (intramedullar metastases), (2) in epidural space with compressive effect on spinal cord, and in (3) leptomeninges. Indirect lesions of spinal cord account for paraneoplastic mielopathy, radiation and toxic mielopathy as complications of radiotherapy (RT) and chemotherapy (CHT) in the treatment of primary malignant disease.

EPIDURAL METASTASES

Epidural metastases of spinal cord (EDM) are far more frequent than intradural metastases and account for about 90% of all metastatic tumors of spinal cord. This tumors are located between two layers of the durra. EDM in more than 80% arise by spreading from metastatic tumor in vertebral body. Malignant cells spread through Batson's venous plexus into vertebral body. This is proven in prostatic cancer, due to very large venous plexus in paraspinal lumbal region. Rarely, EDM are primary located in vertebral posterior arch, and in 10 to 15% they arise by direct spreading of local paraspinal tumors, like Pancoast tumors or retroperitoneal lymphoma. Finally, malignant cells can spread through epidural space also directly, by hematogenous route, witch is rarely seen in malignant hematological diseases (2-4). EDM leads to compressive myelopathy through pressure on epidural venous plexus with its obstruction, compensatory vasodilatation of small arteries and development of vasogenic edema. This leads to ischemia of spinal cord white mater and its infarction.
Malignant tumors that spread metastases in epidural space are lung carcinoma (most frequently small cell type), breast and prostatic cancer, while epidural metastatic spreading is rare in kidney cancer, non Hodgkin lymphoma, multiple myeloma, rectal carcinoma etc. It should be emphasized that in 20% of epidural metastases they can be the first proven region of malignant disease. In childhood epidural metastases are mostly from sarcomas and neuroblastomas.
Most frequent location of epidural metastatic disease is the thoracic region (in about 60%), and than lumbosacral region (30%), while cervical region is very rarely affected. One third of these patients have multiple lesions, so the whole vertebral axis should be examined in case of proven metastatic spinal cord disease.
Pain is the leading clinical symptom in EDM, in about 83% to 96% of patients. It is very mild in the beginning, and increasing in time. Its main characteristic is that it doesn't decrease in resting, while lumboischialgic pain usually decreases in resting during few days period. Pain can be localized, with or without radicular distribution, when dorsal roots are affected. Pain usually precedes to other signs of compressive myelopathy 2 to 4 months that gives us the time for proper treatment.
When the diagnosis of EDM is confirmed, in about 60% to 80% of patients, clinical symptoms and sings are well developed, with motor and sensitive deficit below the lesion, and definitive bladder and bowel impairment. This is the stadium of illness when we can't expect any functional recovery in spite of treatment (5-8).

INTRAMEDULAR METASTASES

Intramedullar metastases (IMM) are relatively rare, compared to EDM, and they account about 4% to 8.5% of all metastatic tumors of CNS. In about 50% of all cases, they are caused by spreading of primary lung carcinoma, and rarely breast or kidney carcinoma, lymphoma or malignant melanoma. Most often they are located in the region of medullar conus (45%), then in the cervical region (34%), and less of all in the thoracic region (20% of cases). IMM are usually seen in late phase of malignant disease.
Symptoms and signs of IMM are very similar to EDM's. Pain is present in about 30% of all patients, changes in sensibility in about 43%, weakness in 30%, and bladder and bowel impairment in 3% of all patients. Very often, in early stage of IMM, we can find signs of Brown-Sequard syndrome of spinal cord hemisection. IMM are very fast growing tumors with quick progression of neurological symptoms, so urgent diagnostic and therapeutic measures are needed. Nevertheless, therapy is rarely successful, and median survival is 3 months.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases (LMM) are multifocal or diffuse infiltration of subarachnoidal space with malignant cells of primary tumor, that can be carcinoma (leptomeningeal carcinomatosis), or hematological malignant disease. Most frequently they appear in lymphomas, leukemia, small cell lung carcinoma, breast carcinoma and malignant melanoma. Rarely they can be seen in renal cell carcinoma, thyroid carcinoma and carcinoid. LMM also can be the result of leptomeningeal dissemination of the primary malignant brain tumors, like medulloblastomas, PNETs, ependymomas or primary CNS lymphomas.
There are several patterns through which malignant cells can reach subarachnoid space. One of them is hematogenic, through small vessels of arachnoid and choroids plexus. Another is penetration of malignant cells from intramedullar dural or osseal metastatic lesions. And the third pattern is perineural route along the neural sheets of spinal roots. In cerebrospinal fluid these cells disseminate further along the craniospinal space.

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Typical clinical manifestation of LMM is the development of different levels of neurological deficits. LMM in spinal channel leads to meningeal irritation with rigidity and strong pain in the neck ant the back. As the consequence of spinal root involvement, paresthesias, palsies, loss of tendon reflexes, and positive Lermitte's sign developed (9-11). Signs and symptoms of increased intracranial pressure with palsies of one or several cranial nerves, may combine in clinical presentation of LMM (12,13).
Prognosis of LMM is very bad, and average survival time in untreated patients is 4 to 6 weeks. The course of that is usually progressive neurological disability.

DIAGNOSIS OF SPINAL CORD METASTASES

Magnetic resonance imaging (MRI) is revolutionary step forward in diagnosis of metastatic disease of spinal cord. Nevertheless, detailed anamnesis and neurological examination are necessary in establishing the diagnosis of metastatic disease of spinal cord. In cases of unknown primary malignancy it is important to evaluate all blood analyses, standard thoracic radiography, and ultrasonographic examination of neck, abdomen and pelvis. Sometimes radionucleid examination of the osseal system may be necessary. MRI is the most important diagnostic tool in assessment of spinal cord metastasis (14,15). T1W, and T2W without and with contrast medium, has to be performed in axial, sagital and coronal planes. Vertebral metastases are usually hypointense in T1W sequence and hyperintense in T2W sequence. Since extradural metastases usually destroy the shape of vertebral body, compressing the dural sheet, they can easily be visualized on T2W sequence. There is usually good enhancement of these lesions when paramagnetic contrast is used. LMM is excellently visualized on T1W sequence after application of contrast medium (15-17).
Lumbal puncture with CSF analyses can reveal the presence of malignant cells. Sometimes, cytological evaluation and findings of malignant cells in CSF, are the only aprovement of existing LMM. MRI however can confirm the presence of LMM without findings of malignant cells in CFS. In diagnostically unclear cases the combination of these diagnostic procedures is proposed (13,17). In CSF one can usually find pleocytosis, hiperproteinorrachy and hipoglycorrachy. The determination of tumor markers in CSF and serum can be also helpful. In all cases in witch the concentration of CSF marker is more than 1% of serum concentration the diagnosis of LMM is highly predictable. Different imunohistochemical and PSR analyses can help in confirming the diagnosis of LMM (18). The biopsy of meninges can be occasionally performed only in diagnostically unclear cases. Differential diagnosis of spinal cord metastases is numbered in Table 1.

Table 1. Differential diagnosis of spinal cord metastases

Primary intramedulary tumor
Extramedulary tumor
Postirradiation myelopathy
Toxic myelopathy due to chemotherapeutic agents
Paraneoplastic myelopathy
Spondylotic myelopathy
Spinal arteriovenous malformations
Transverse myelopathy
Spinal epidural haemathoma
Spinal epidural abscess
Amiotrophic lateral sclerosis
Intervertebral disc herniation
Spondylodiscitis
Osteoporosis

THERAPY FOR SPINAL CORD METASTASES

The aims of therapy for spinal cord metastasis according to severity of disease are: (1) pain relief, and (2) preserving the motor function of extremities and sphincters. Symptomatic therapy involves administration of corticosteroid and analgetics, while causal therapy demands surgery, radiotherapy and chemotherapy.

Symptomatic therapy

Corticosteroids decrease the pain and sometimes even improve the neurological deficit due to their antiedematose ability. There are particularly efficient when combined with radiotherapy. Dexamethasone is the most commonly used corticosteroid although there is still no agreement regarding to optimal doses for these medication. If its administration is necessary for prolonged period of time, usually doses are 16 mg daily, and not more than 32 mg daily.
Analgetics that are usually used in metastasis spinal cord disease are nonsteroid antireumatics at the beginning, and opioids in progressive form of disease.
Symptomatic therapy also includes proton pump blockers, prophylactic therapy for deep vein thrombosis, antibiotic and constipation therapy.

Causal therapy

Radiotherapy is the basis for treatment of metastatic spinal cord disease. In many cases it disables further progression of tumor and worsening of the neurological disability. The efficiency of radiotherapy depends on radiosensitivity of the primary malignancy.
Spinal cord metastases from myelomas, lymphomas, breast carcinomas, prostatic carcinomas, and small cell lung carcinomas are radiosensitive, while metastases from melanoma and renal cell carcinoma are radioresistant.
Usual radiotherapy regimen is 39, 42 or 42-48 Gy in 3 Gy fractionation daily. Side effects of this regimen are dysphagia, diarrhea and pancitopenia (if the large part of spine is irradiated). The most severe complication of this kind of therapy-spinal cord radionecrosis develops in 1% to 5% of patients (20,21). Improvement in radiation therapy with very thin radiation fields, decrease this kind of complication.
Systemic chemotherapy should be administered only in chemosensitive primary malignances (14,23), like lymphomas, neuroblastomas, breast carcinomas and prostatic carcinomas. In LMM chemotherapy is administered only intrathecally (methotrexate or cytarabine), or in combination with systemic chemotherapy and radiotherapy.
Surgical treatment is indicated only in extradural metastasis. Anterior or posterolateral approaches have to be performed with spine stabilization procedures, since laminectomy is proven to worsen neurological deficit (24-26). The replacement of vertebral body can be accomplished in selected group of patients.

PROGNOSIS

Prognosis of spinal cord metastatic disease is generally poor. In the moment of established diagnosis, the neurological deficit is usually severe, and efficacy is poor. Expected survival period in these patients is 4 weeks to 6 months.

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Treatment complications in patients with brain metastases

KEYWORDS: Brain Neoplasms; Neoplasm Metastasis; Surgery; Radiotherapy; Radiation Injuries; Drug Toxicity; Antineoplastic Agents; Intraoperative Complications

The treatment of brain metastases usually consists of the combination of open surgery (S), stereotactic radiosurgery (SRS), radiotherapy (RT), and chemotherapy (CHT), especially in patients with previously treated primary malignancy. All of these modalities of treatment have their advantages, disadvantages and complications. Sometimes their combination (RT with chemotherapeutic or biological agents) might be the cause of the neurotoxicity.
Modern diagnostic facilities enable us to distinguish between the radiation lesions of the brain from the tumor recurrence. Among them the most important are magnetic resonance (MR) spectroscopy, positron emission tomography with ^{18}F-labeled fluorodeoxyglucose (PET-FDG), and thallium 201 spectroscopy (single-photon emission computerized tomography – SPECT.
Sometimes, complications of the therapy can be so severe that they become life-threatening or fatal.

COMPLICATIONS OF OPEN SURGERY FOR BRAIN METASTASES

The *advantages* of open surgery over other treatments for brain metastases are: (1) immediate elimination of the effects of increased intracranial pressure, and direct irritation of the surrounding brain, (2) histological confirmation of metastases, because as many as 15% of patients with clinical diagnosis of metastasis may in fact have nonmetastatic lesions, (3) local cure if all tumor cells are removed (1). The main *disadvantage* of open surgery for brain metastases is potential intraoperative and postoperative problems including bleeding, wound infection, worsening of the preoperative neurological deficit, myocardial infarction, pneumonia, pulmonary embolism, sepsis etc. Some of these complications are due do direct surgical lesion of the surrounding brain, and some depend on general health of the patient.
With modern neurosurgical facilities expected *morbidity* after open surgery is 10% (only 5% neurosurgical and neurological) and mortality 0.5% to 3%, although some recent series report no mortalities at all (2-4). Stereotactic biopsy for which can only provide histological diagnosis of intracranial tumor in clinically unclear cases have the morbidity and the mortality of 3% of all cases (1). Surgery with postoperative whole brain radiation therapy (WBRT) significantly prolongs survival of the patients with brain metastases.

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COMPLICATIONS OF RADIOTHERAPY FOR BRAIN METASTASES

Pathogenesis

Radiation, causes breakage of deoxyribonucleic acid (DNA) strands, leading to loss of function and cell death. In the mitotic phase cells are most vulnerable to DNA damage. The effect of radiation on healthy tissue is greatest on actively proliferating and undifferentiated cells. The brain, spinal cord, cranial nerves, brachial and lumbosacral plexus, and peripheral nerves may experience direct damage whereas damage to blood vessels and hypothalamic-pituitary axis may result in indirect damage to the nervous system (5). It should be mentioned that X- rays, alpha particles and microwaves cause blood-brain barrier (BBB) damage which can occur as late as several years after RT, and it is probably due to capillary occlusion secondary to progressive thickening of the basal membrane, ischemic tissue necrosis and abnormal proliferation of new capillaries in the irradiated regions of the brain (6).
Two hypothesis – the glial hypothesis and the vascular hypothesis – have been posed do explain radiation damage to healthy brain. Damage, however occurs to both glial cells and blood vessels, but what determines their relative contribution is unknown (5).

Epidemiology

The incidence of neurotoxic side effects of radiotherapy, especially irreversible late complications, is difficult to define as studies on this subject vary greatly in the definitions used, the populations studied, and the duration of follow up. The risk of developing a severe late-delayed encephalopathy caused by WBRT for brain metastases has been estimated to range between 1.9% to 5.1% (7). It is estimated that focal radiation necrosis occurs in 5% to 15% of patients receiving whole brain radiation of 60 Gy in 30 fractions (8).

Risk factors

There are some predisposing – risk factors for development of delayed radiation damage. They can be subdivided into host- and treatment-related factors and probably overlap incompletely for radiation necrosis and leucoencephalopathy. *Host-related factors* are: (1) age – greater than 60 and in some series even 40 years, (2) preexistent white matter disease like multiple sclerosis, (3) vascular risk factors like hypertension, diabetes, systemic disorders, (4) tumor pathology – the incidence of delayed encephalopathy in patients with primary CNS lymphoma is higher than in other tumors, (5) individual susceptibility to radiation damage – genetic predisposition (9-11).
Treatment-related factors include: (1) total dose of RT / radionecrosis occurs more frequently with higher doses – patients treated with more than 50 Gy, (2) RT fraction dose – daily doses greater than 2 Gy significantly increase risk of cognitive damage and radiation necrosis (7,9,12), (3) radiation volume – WBRT gives three- to fourfold increased risk of delayed encephalopathy (10,13), (4) total duration of therapy, and (5) additional chemotherapy – neurotoxicity can increase with some chemotherapeutic agents like methotrexate, nitrosureas, vincristine, and cytosine arabinoside.

Clinical syndromes of direct radiation damage to the brain

Radiation-induced damage to the brain may occur at a different time interval following radiation. All clinical syndromes may be divided into three groups of signs and symptoms: (1) acute encephalopathy, (2) early-delayed encephalopathy, and (3) later-delayed encephalopathy.

Acute encephalopathy

It usually develops within 2 weeks of the start of treatment and is caused by vasogenic edema after disruption of BBB. The possibility of occurrence of acute encephalopathy increase with large fraction dose (over 3 Gy), large volume of brain treated and increased intracranial pressure. Patient's com-

plaints are usually somnolence, nausea, vomiting, loss of appetite, worsening of preexisting neurological deficit. Computerized tomography (CT) of the brain shows usually progression of the focal brain edema. This is reversible disorder, and corticosteroids are the treatment of choice.

Early-delayed encephalopathy

This radiation damage may occur one to 6 months after completion of RT, and it can be difficult to distinguish from early tumor progression, especially in high grade glioma, since CT and MR images may reveal an increase in the contrast-enhancing area and surrounding edema (14) (Figure 1). The neurological worsening due to this encephalopathy is reversible within a few months and corticosteroids again are the treatment of choice, only in this case the duration of corticosteroid therapy has to be prolonged for several months.

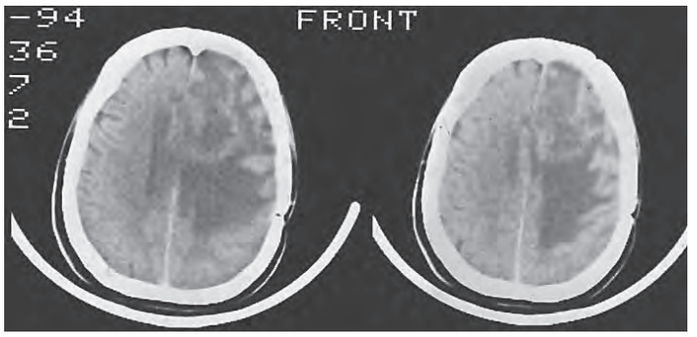

Figure 1. Focal early-delayed encephalopathy 6 months after the radiation therapy for right frontal oligoastrocytoma grade II

Late-delayed encephalopathy

This clinical and radiological syndrome occurs months to years after RT. It is clinically characterized by progressive mental slowing, deficits of attention and memory, gait ataxia, urinary incontinence, apathy, and pyramidal or extrapyramidal signs (5). Cognitive symptoms may progress to a severe dementia. Radiologically, cerebral atrophy and white matter changes occur after months to years, and abnormalities tend to increase up to 3 years after treatment. The cerebral atrophy usually occurs first, with ventricular dilatation being more prominent than cortical atrophy. White matter changes follow, initially predominantly in the periventricular area, but in severe cases confluent lesions can be seen throughout the white matter (12,13) (Figure 2).

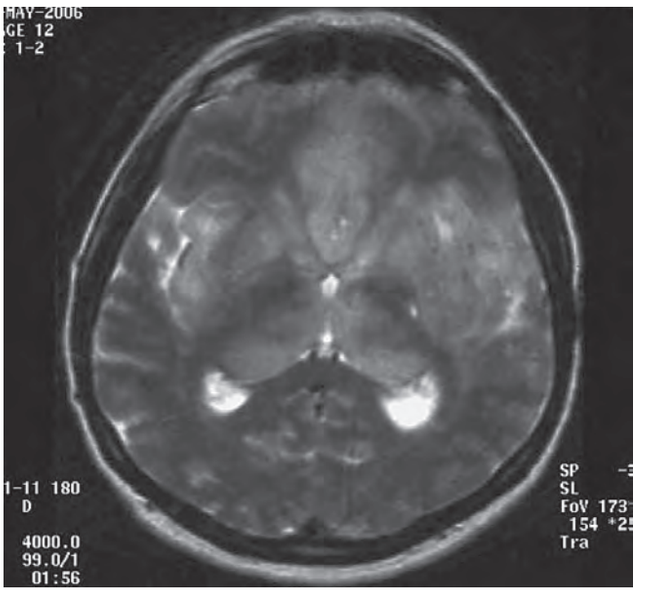

Figure 2. Late-delayed encephalopathy in patient 2 years after radiotherapy for low grade astrocytoma of the left temporal lobe

Histologically, various changes have been found, but they may be categorized into two main groups: (1) diffuse axonal and myelin loss with the multiple disseminated small foci of necrosis, and (2) diffuse spongiosis of the white matter with vacuoles displacing the normal myelin sheets (15). In patients treated by focal radiation with fraction doses not exceeding 2 Gy for a glioma the risk of cognitive decline is probably low, but increases with the time especially after 4 to 5 years (16).

Focal radiation necrosis

Radionecrosis is the most complicated side effect of radiotherapy for brain tumors. It may appear after an interval ranging from several months to many years (8). The incidence of focal radionecrosis has increased with implementation of stereotactic radiosurgery. It is extensive foal white matter necrosis in combination with hyalinized thickening of blood vessels with fibrinoid necrosis, narrowing of the lumen and endothelial proliferation, and also thrombosis of vessels or hemorrhages from teleangiectatic vasculature. Functional imaging (PET, SPECT) shows hypometabolism in the area of radionecrosis. Clinical signs and symptoms may vary from seizures, dementia, focal neurological deficit like hemiparesis to impairment of consciousness due to increased intracranial pressure. It is usually fatal (Figure 3).

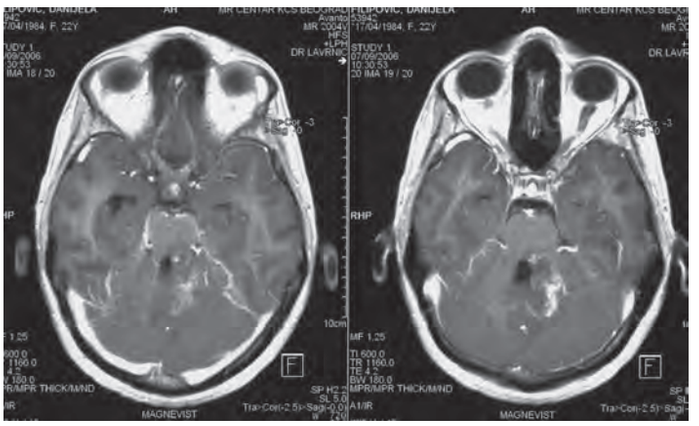

Figure 3. Radionecrosis of brain stem and cerebellum, according to MR spectroscopy in patient 5 months after the irradiation for pineal anaplastic astrocytoma

Mineralizing angiopathy

This is usually asymptomatic postirradiation complication. It can be demonstrated on CT like multiple subcortical calcifications. It is more radiological than clinical phenomenon, and may bee seen in children after CNS irradiation for acute lymphatic leukemia (5).

Indirect radiation damage to the brain

Radiotherapy can cause *vascular damage* with delayed effects on all blood vessels within the radiation field that can lead to teleangiectasia, hemorrhage, cerebral infarction or development of moya-moya disease. Accelerated atherosclerosis is seen most frequently in the carotid artery.

Usually overlooked late complication of cranial RT is endocrine dysfunction caused by damage to the hypothalamic-pituitary axis. Growth hormone is the most sensitive, and the thyroid-stimulating hormone the least sensitive, with sex hormones and adrenocorticotropic hormone in between.

Irradiated patients may develop *secondary tumors* in the nervous system even after low-dose radiation. Three principal types of tumors have been reported: (1) meningeomas in about 70% of cases, (2) glioma in 10% to 20%, and (3) sarcoma, also in 10% to 20%.

Therapy for postirradiation brain damage

Treatment of acute and early-delayed radiation damage is not always necessary, because they are self-limiting. However, when necessary corticosteroids (dexamethasone) are the treatment of choice.

On the other hand, late-delayed radiation injuries can be very difficult, if not impossible to cure. Corticosteroids, anticoagulants, hyperbaric oxygen therapy, acetylcholinexterase inhibitors, and cognitive training are the possibilities for treatment, but with uncertain effects.

COMPLICATIONS OF CHEMOTHERAPY FOR BRAIN METASTASES

Neurological toxicity during treatment for cancer is common. The risk that neurological complications during the treatment will appear increases with: (1) large cumulative doses of neurotoxic agents, (2) combination of multiple neurotoxic agents, and (3) high-dose radiotherapy (17). Signs and symptoms highly different depending on the (1) involved part of the nervous system (central or peripheral, cerebral or cerebellar, spinal cord etc), (2) the route of delivery (systemic, intrathecal), (3) the dosage, and (4) concomitant therapy. They can vary from sensitive disorders to severe motor deficit of extremities, from ataxia to severe parkinsonian disorders, from mental changes and psychiatric disorders to the loss of consciousness and seizures.

Alkylating agents have modest neurotoxicity.
The encephalopathy caused by *ifosfamide* may begun within hours or as long as 5 days after beginning the drug and usually resolves completely within several days of conclusion of treatment. It occurs in about 20% of patients. Oral administration of this drug is more neurotoxic than the intravenous form.
Nitrosureas (BCNU and CCNU) are most often used to treat primary brain tumors, multiple myeloma and lymphoma. When BCNU and CCNU are administered at recommended doses and routes of administration, they are without neurotoxicity.
Procarbazine is used in treatment for primary brain tumors in combination with vincristine and CCNU (PCV therapy). It can cause lethargy, depression, agitation or psychosis, and together with vincristine peripheral neuropathy.
Busulfan is the agent that crosses BBB easily and achieves high concentrations within the cerebrospinal fluid (CSF). About 10% of patients who receive high-dose therapy will experience focal or generalized seizures.
Hexamethylmelamine is an atypical alkylating agent. The peripheral neuropathy is the most common form of neurotoxicity, while CNS side effects include confusion, depression, sometimes hallucinations, dysphagia, personality changes etc.
Cisplatine and its analogues are important and unique class of chemotherapeutic agents. *Cisplatin*-induced neurotoxicity can manifest as sensory peripheral neuropathy, autonomic neuropathy, encephalopathy, retrobulbar neuritis or retinal injury (18). The incidence of neurotoxicity approaches 100% depending on the individual dose level. Toxicity most often occurs in the rage of cumulative dose of 300 to 500 mg/m^2. Concurrent use of cisplatin and paclitaxel has shown efficacy in the treatment of advanced breast cancer, but the combination therapy has also demonstrated increased potential for neurotoxicity.
Oxaliplatine has a higher degree of antitumor activity than cisplatin. The dose-limiting toxicity of this agent is sensory neuropathy which takes two forms: (1) acute one (laryngopharyngeal spasm with dysphagia and dyspnea), and (2) as typically seen with cisplatin affects the extremities.
Carboplatin is the least neurotoxic of available platinum compounds.

Antimetabolites represent attractive targets for antitumor chemotherapy because of their role in the synthesis of the nucleotide precursors of DNA.
The profile of neurotoxicity for methotrexate *(MTX)* depends on the route of delivery, dosage and combination therapy. When delivered intrathecally three different syndromes have been described: (1) acute chemical arachnoiditis with severe headache, neck rigidity, vomiting, and fever (10% to 50% of patients), (2) subacute form of neurotoxicity with paresis, cranial nerve palsies, seizures and coma (10% of patients), and (3) chronic demyelinating encephalopathy which usually occurs in children months to years after receiving intrathecal MTX. *Transverse myelopathy* is less common complication, signs and symptoms occur 30 minutes to 48 hours after treatment with low back and leg pain followed by rapidly ascending flaccid paraparesis. This syndrome most often occurs in patients receiving simultaneous radiotherapy or frequent intrathecal injections (18).
5-Fluorouracil may cause cerebellar dysfunction with gait ataxia, nystagmus and dysarthria, because 5-FU readily crosses the BBB and its highest concentrations are found in the cerebellum.
Cytarabine has neurological toxicity with high-dose regimens (more than 1g/m^2 in multiple doses). Clinical manifestations may be different, and cerebellar dysfunction appears in 15% of patients.
Pentostatin in high doses can cause seizures in 60% of cycles. Current regimens using lower doses have resulted in less neurotoxicity (15%).
Antimicrotubule agents – vinca alkaloids are used in combination with other agents for many different tumor types, particularly in the pediatric population. The principal and dose limiting toxicity of *vincristine* is neurotoxicity in the form of a symmetrical, mixed, sensory-motor and autonomic polyneuropathy. Neurotoxicity is rare with the other vinca alkaloids, *vinblastine*, *vindesine*, and *vinorelbine*.
The *taxanes* have an impressive clinical activity in ovarian and breast cancer. Paclitaxel produces peripheral neuropathy which is predominantly sensory, and is dose-dependent phenomenon. Sensorimotor neuropathy is less common with *docetaxel*.

Hormonal agents

Corticosteroids are the first line of defense in brain metastases. However, in high doses they can produce neuropsychiatric symptoms that usually resolve after discontinuation of the therapy.
Tamoxifen may cause visual complaints or retinal changes, but neurotoxicity is not common.

Biological agents

A high incidence of neuropsychiatric toxicity has been appreciated in patients treated with recombinant *interpheron alpha-2b*. Interleukin *IL-2* penetrate BBB and may cause neurotoxicity in the form of hallucinations, disorientation, agitation, combativeness, and seizures.

CONCLUSION

According to all outnumbered complications of therapy for brain metastases and primary cancer the decision of treatment regimen must be individually – based one, for every single patient.

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