

A Series of 3 Cases of Cerebral Glioma with Intraspinal Dissemination: Evaluation and Review of the Literature

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Abstract: Extra-cranial metastases of malignant gliomas such as glioblastoma (GBM) are rare. 3 Cases were reported in this evaluation with spinal leptomeningeal metastasis in patients suffering from cerebral glioma / glioblastoma multiforme with radicular pain in the extremities.

Patients and Methods: The first patient (male, 34 years old) suffered from hemiparesis 2 years after the craniotomy and micro-neurosurgical extirpation of astrocytoma WHO II° then anaplastic astrocytoma WHO III° right frontotemporal. The second patient (female, 43 years old) developed a spinal channel metastases of a brain stem GBM approximately 9 months after surgical resection and radio-chemo-therapy. In the third case (male, 21 years old), initially a thoracic spinal intramedullary GBM was operatively excised with a postoperative paraplegia. In the following period of time the diagnosis of a cerebral GBM was performed by a stereotactic biopsy method. All specimens in the 3 cases were confirmed histopathologically.

Results: In the first patient, who was initially operated for astrocytoma WHO II° and then later the recurrence was diagnosed after excision as anaplastic astrocytoma WHO III°, for him a lumbar spine hemilaminectomy was performed after a concomitant radio-chemotherapy and stereotactic irradiation, whereas after the surgery a further irradiation therapy was necessary. A significant regression / improvement of the neurological symptoms was registered. Intraspinal metastases of the second patient were treated by irradiation therapy with significantly withdrawal of the symptoms, which was necessary due to reduced clinical and deterioration of the neurological state of the patient. A Partial improvement of the neurological symptoms was observed in the third patient during and after the chemotherapy.

Discussion: Reported cases of intraspinal dissemination from the primary intracerebral glioma tumor have varied and as in the presented cases in this series, intraspinal metastases have also been observed in patients with stable intracerebral disease. Typically, the incidence of symptomatic intraspinal metastasis has been lower than the incidence observed post mortem because patients do not survive long enough for small tumor implants to develop into symptomatic lesions. However, with improved outcome observed from newer treatments and improved diagnostics the incidence is likely to increase in the future.

The management of the three patients in this series was optimized through the modern diagnostic measures leading to improve the clinical condition despite the bad overall prognosis.

Conclusions: Spinal spread of malignant glioma should be considered during care and follow-up investigations in patients with this diagnosis and with spinal symptoms. The surgical therapy seems to offer benefits for these patients. The radio-chemotherapy can be helpful in this cases as well. Further examinations and studies are necessary to be performed in order to understand more about the etiology, clinical course, interrelationship and coherence of these findings.

Keywords: Cerebral glioma, glioblastoma multiforme, anaplastic astrocytoma, intraspinal dissemination, malignant brain tumors, extra-cranial metastases, cerebrospinal fluid (CSF), intracranial pressure (ICP), symptomatic intraspinal space occupying lesion (SOL).

1. INTRODUCTION

Intraspinal (leptomeningeal or intramedullary) metastases from primary intracranial gliomas have been well documented in several clinical and pathological series (1–5, 9-13, 20, 23, 40, 79-90, 109-114). Post-mortem and cytological incidence of meningeal and cerebrospinal fluid (CSF) dissemination of up to 40 % has been demonstrated in these studies (19, 23, 56, 76, 93, 101, 105, 109-113).

Symptomatic intraspinal metastases in patients with primary intracerebral gliomas occur rarely (34, 58, 90, 99-107).

However – roughly 1–5 % in published series (6–9, 7, 9, 21, 45-49, 77, 90, 101) with the reduced incidence of symptomatic metastases primarily attributed to poor survival in this group of patients.

In this case series, three patients with symptomatic intraspinal leptomeningeal and intramedullary metastases from intracranial glioma / glioblastoma were reported. All three patients were treated initially in Hamburg / Germany.

The clinical findings, radiographic evaluation, treatment and subsequent clinical course of these patients were evaluated in this retrospective study.

The neurosurgical management of the patients two and three was started in our centre. The clinical data could not be completed, as they were continuing the treatment at other neurosurgical departments.

2. CASE (1)

Patient J. Y. , male, 34 years old, civil engineer, no history of alcohol, no cigarettes, no drugs. No history of any chronic diseases. He was presented initially in 02 / 2002 with intermittently occurring headache, giddiness and significant symptomatic epilepsy. Patient was treated symptomatically, he was referred to the neurologist and then he underwent the neurosurgical interventions and further radio-chemotherapy. Patient died in December / 2010.

See figures 1- 8 below for the clinical course including all therapy and treatment steps for the patient.

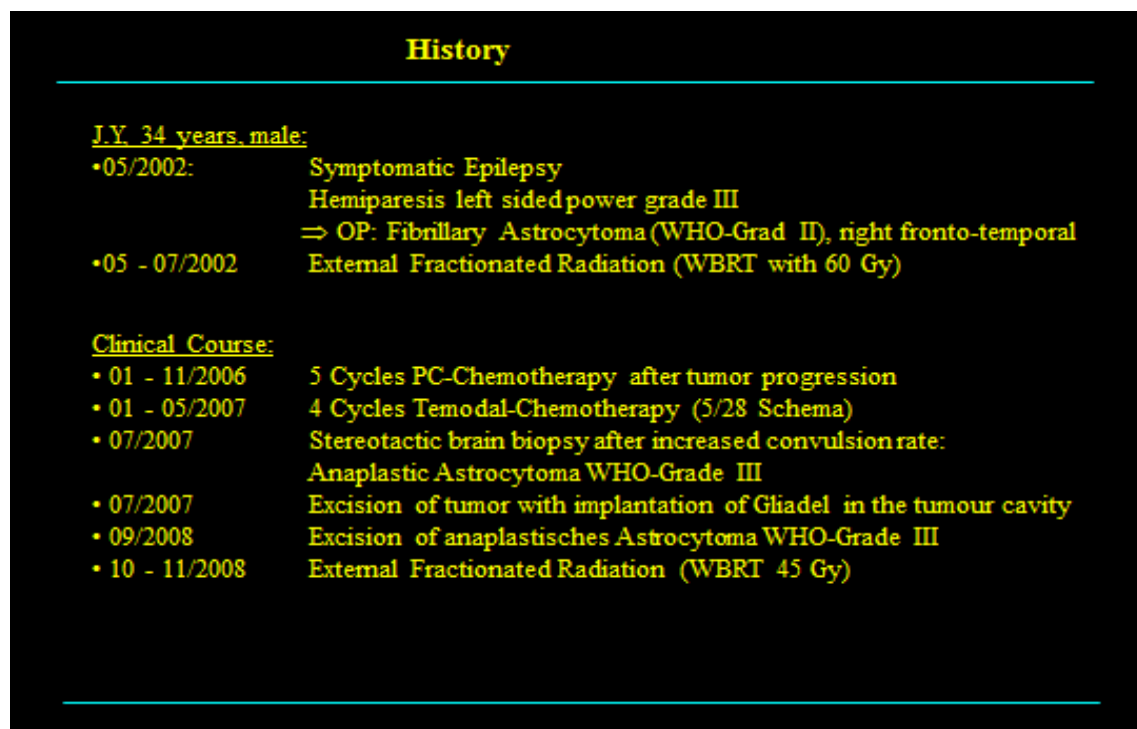


Figure 1: History and initial clinical presentation with symptomatic epilepsy; craniotomy and tumor excision (Fibrillary Astrocytoma WHO II°); external fractionated radiation; chemotherapy; stereotactic brain biopsy in 07 / 2007 after increased convulsion rate; diagnosis of Anaplastic Astrocytoma WHO III°; excision of tumor with implantation of Gliadel wafers; in 09/2008 excision of tumor after recurrence with same grading; 10 – 11 / 2008 External Fractionated Radiation

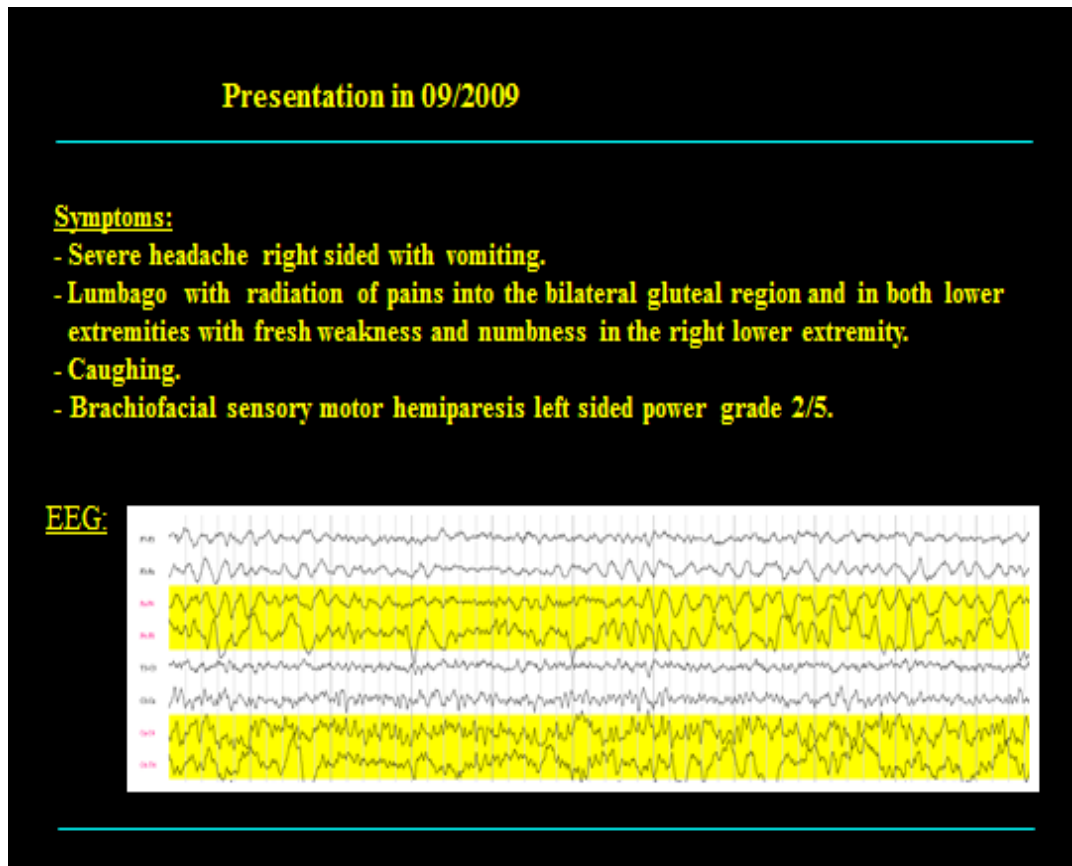


Figure 2: Presentation in 09 / 2009 with severe right sided headache, vomiting, coughing and lumbago with radiation of pains into bilateral gluteal region and lower extremities with fresh weakness and numbness in the right lower extremity, brachiofacial sensory motor hemiparesis left sided.

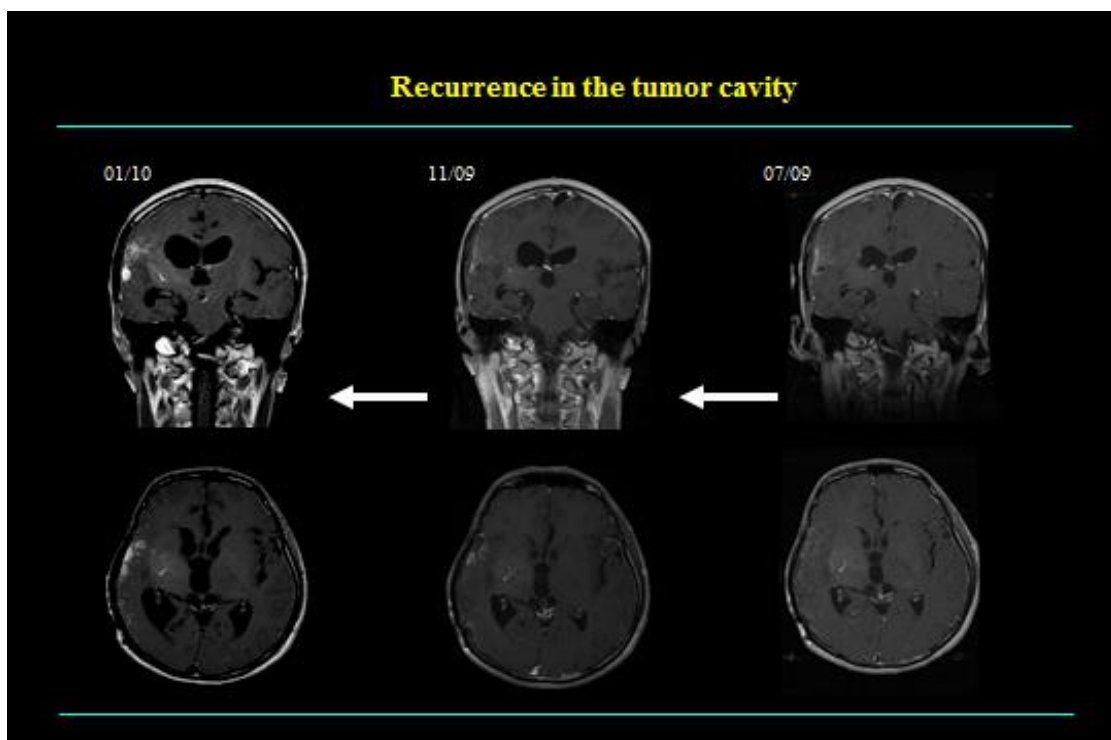


Figure 3: Recurrence in the tumor cavity (see progression from 07/2009 till 01/2010).

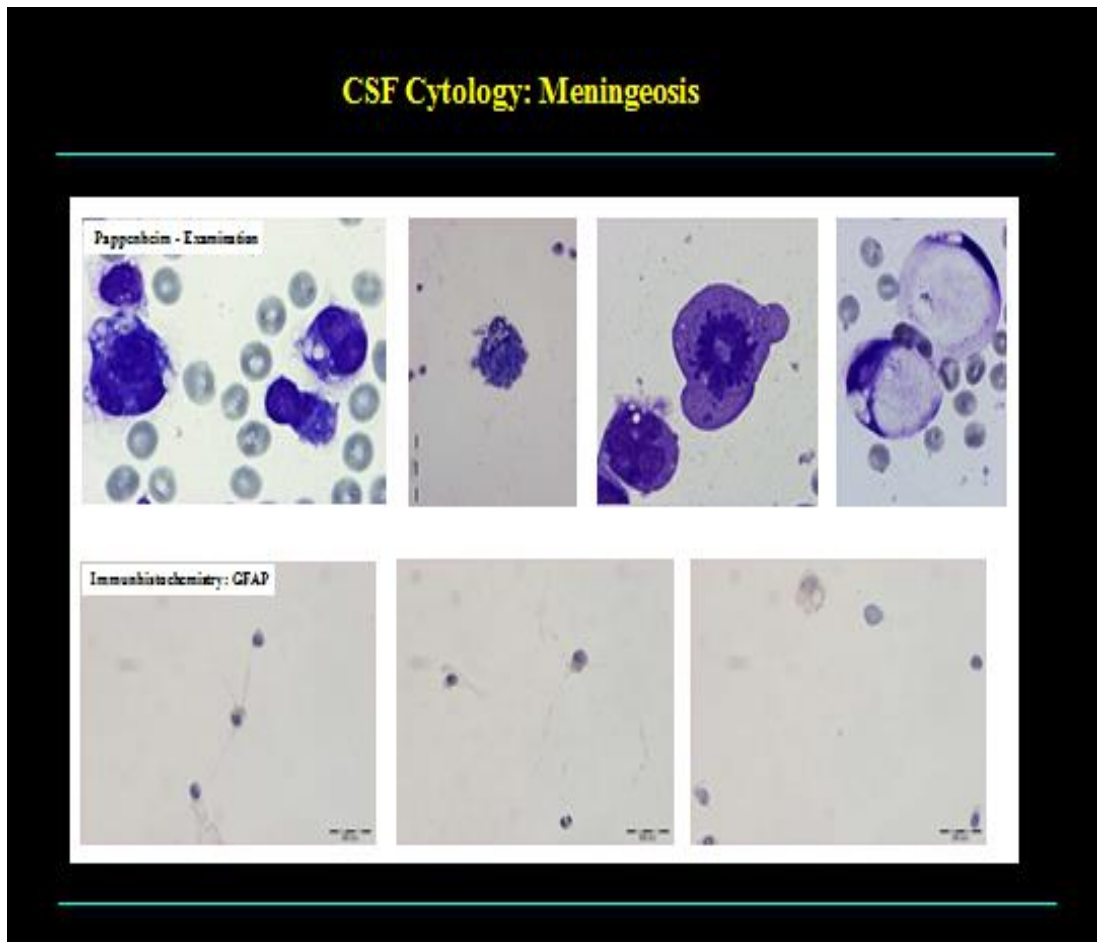


Figure 4: CSF cytology with meningeosis.

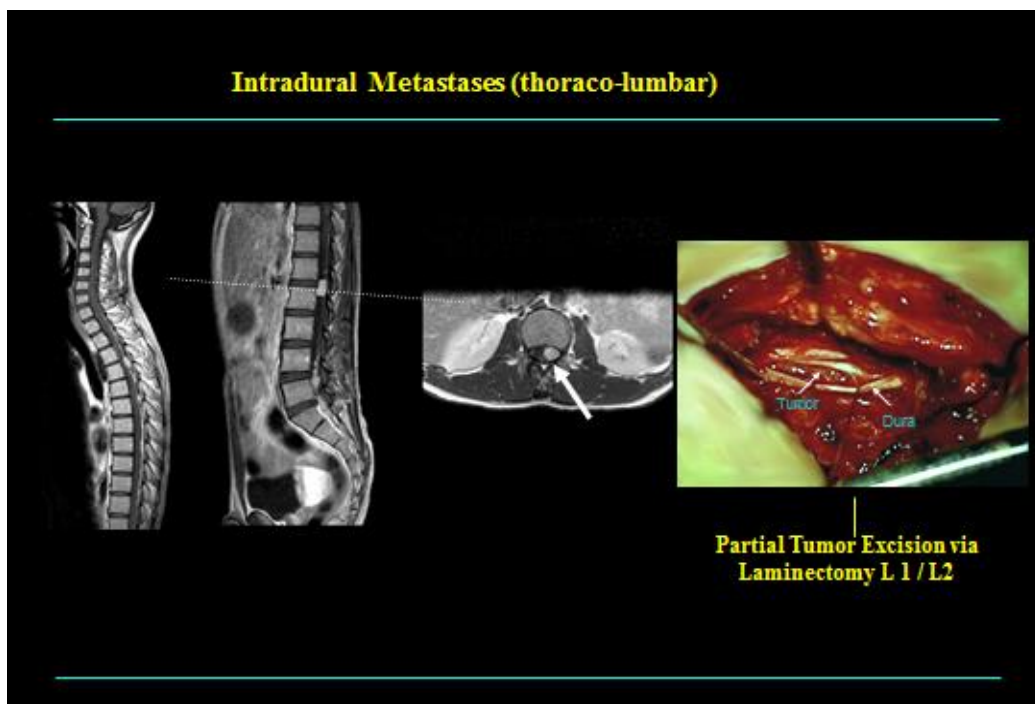


Figure 5: Intradural spinal metastases.

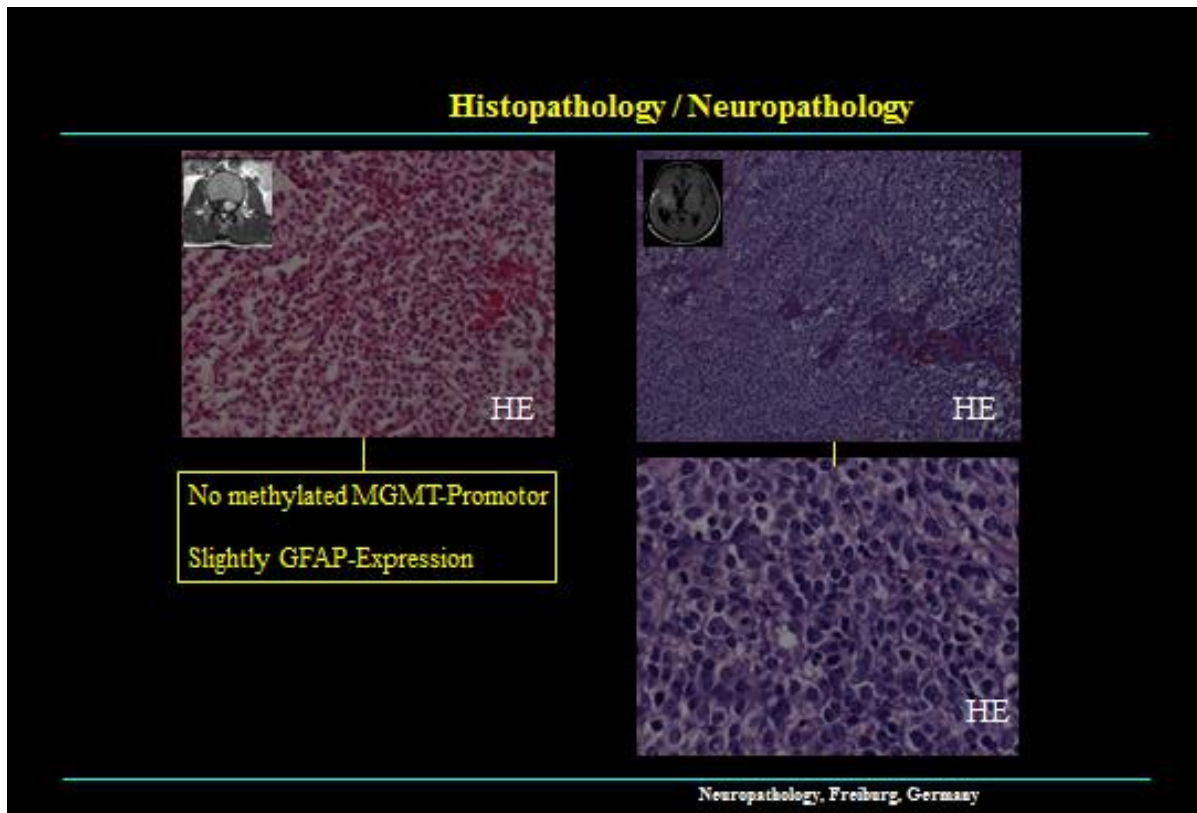


Figure 6: Histopathological / neuropathological evaluation with slightly GFAP expression and no methylated MGMT promotor.

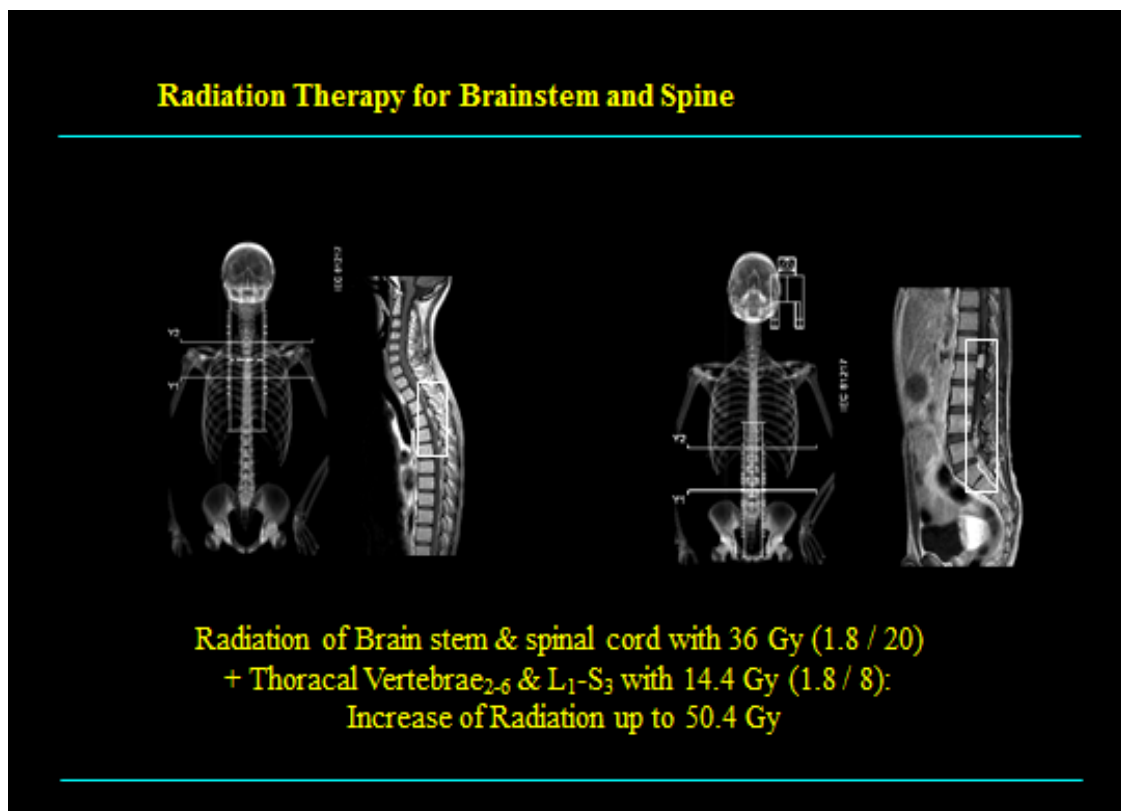


Figure 7: Radiation treatment for brain / brain stem and thoracal and lumbar vertebrae after the spinal surgical intervention.

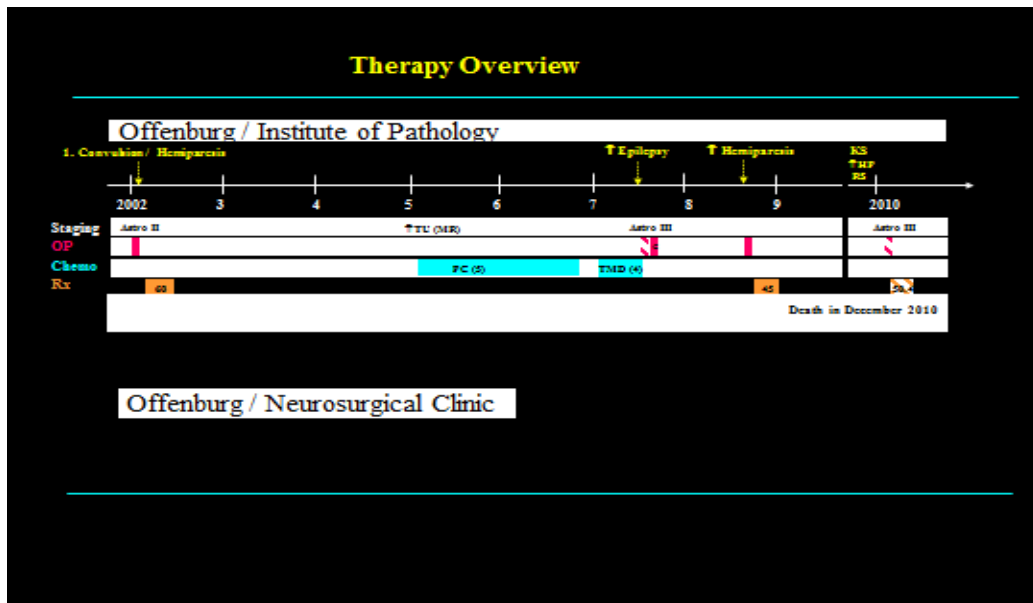


Figure 8: Overview of the therapy of the patient.

The clinical data about the other two cases was similar to that data of case one. The further treatment of the other two patients was continued in another neurosurgical centres.

3. DISCUSSION

Herbert H. Engelhard, and Luke A. Carsten from the University of Illinois at Chicago, described in 2005 the “leptomeningeal metastasis of primary central nervous system (CNS) neoplasms”. (34-40) According to their evaluation, leptomeningeal dissemination of primary CNS tumors varied widely by histologic subtype. In certain tumors including medulloblastoma, ependymoma, germ cell tumors, and primary CNS lymphoma, seeding of the cerebrospinal fluid space is a critical factor in determining stage, prognosis and appropriate therapy. Other tumor types, such as glioma, may have radiographic evidence of leptomeningeal metastases without clear impact on prognosis or therapy.

As discussed in previous chapters, many types of malignant tumors originating outside the central nervous system (CNS) are known to metastasize to the leptomeninges, including lymphomas, leukemias, and carcinomas from various primary sites. The spread of primary CNS neoplasms through the leptomeningeal space may be a fairly frequent occurrence, but has not been thoroughly studied, especially in adults. In 1837, Ollivier reported the autopsy findings of a patient with a cerebellar tumor that had spread throughout the leptomeningeal space of the cisterna magna, referring to it as "sarcomatous meningitis".(78-86) This likely represents the first reported case of a primary CNS tumor with leptomeningeal metastasis (LM). The propensity of medulloblastomas to spread via cerebrospinal fluid (CSF) pathways was known in the mid- to late 1800's, and was well described in the early 1900's by Cushing. (2, 7, 9- 14, 56-58, 98-106). While the classification of primary CNS tumors is extensive, a medulloblastoma is an embryonal tumor of the posterior fossa and in a category that is distinct from the gliomas, the major sub-categories of which include astrocytoma, oligodendroglioma and ependymoma (3, 22, 25-29). Dissemination of high-grade glioma cells through the leptomeningeal space can be termed "leptomeningeal gliomatosis". (17, 26, 78, 79, 83, 89-93, 106-114). Primary diffuse leptomeningeal gliomatosis (PDLG) is an extremely rare disease entity which shares features with LM from CNS neoplasms. Patients usually present with non-focal symptoms, such as headache or seizures, then experience a progressive, downhill clinical course.(28-32) Alterations of mental status, papilledema, hydrocephalus, meningismus, cranial nerve palsies and symptoms and signs from spinal involvement may also be seen. With this disease, no distinct primary tumor (or source for the seeding) can be found, even at autopsy. While magnetic resonance imaging (MRI) may show meningeal enhancement with gadolinium, CSF cytology is usually negative. In patients with PDLG, biopsy of an enhancing area of the meninges may lead to diagnosis.(29-33) Treatment is usually not very effective, although a complete remission in one case has been reported with the use of corticospinal radiation, multidrug systemic chemotherapy, ventricular and lumbar

shunting, and intrathecal methotrexate. (33-35, 45-55) In PDLG, malignant cells are presumed to arise from ectopic rests of glial tissue outside the pial plane of the CNS with resultant dissemination along the leptomeninges. (21, 29, 40-43) Varying lineages of glial cells may be involved, and the disease may occur anywhere within the leptomeningeal space. (32) PDLG has even been reported to be a cause of "sudden death". (15, 27, 89, 99, 111) As imaging of the neuroaxis improves, smaller primary sites may be detected and the diagnosis of PDLG may become even more rare. The meninges themselves (leptomeninges and pachymeninges) can give rise to both malignant and benign tumors (such as meningiomas). (3-9, 12-18, 22-25, 77) The propensity for even benign meningiomas to spread along the dura (and thus the need to resect infiltrated dura along with tumor removal) is well known.

Lachance DH, O'Neill BP et al. described primary leptomeningeal lymphoma and reported 9 cases and showed diagnosis with immunohistochemical analysis, (66).

Primary leptomeningeal lymphoma is a rare primary tumor of the leptomeninges. (56, 66, 69)

Herbert Engelhard et al described 2005 and 2015 in his book leptomeningeal metastasis of primary central nervous system (CNS) neoplasms. Several topics were reviewed including:

1) the possible mechanisms of leptomeningeal spread from CNS tumors, 2) the spectrum of CNS tumors found to lead to LM, both in children and adults, 3) the incidence of LM from CNS tumors, 4) the clinical presentation and diagnostic evaluation of these patients and, 5) treatment options, follow-up measures and prognosis. Regarding mechanisms of metastasis, three different pathways have been suggested through which cells from a CNS tumor might gain access to the leptomeningeal space. (7-16, 19-39) First, a tumor might be in direct contact with the CSF pathways, as in the case of a medulloblastoma or intraventricular tumor. (3, 41, 90-92, 105) In this situation, tumor cells could be "shed" directly into the CSF. Second, tumor cells might invade the leptomeningeal space by moving through and or displacing normal brain parenchyma, then eroding through the pia mater or ependyma, i.e. direct extension. This is currently believed to be the most likely mechanism through which tumors gain access to the leptomeningeal space. Proximity to the CSF pathways would then be a "risk factor" for the occurrence of such erosion, and dissemination. Nishio et al performed an autopsy study of 26 patients with different types of brain tumors and found that focal ependymal defects were often present, especially in patients with hydrocephalus. (79, 81-88, 90, 98, 114) A third possibility is that tumor cells might be directly "inoculated" into the CSF at the time of a surgical procedure, such as a craniotomy or CSF shunt. Many years ago, support for the "surgical inoculation" theory was found in studies which examined the proportion of preoperative versus postoperative CSF samples with positive cytology in patients undergoing surgery for medulloblastoma.

More recently, (34, 36, 49, 51, 56-59), Elliott and colleagues did a retrospective review of 51 patients with malignant glioma studying both surgical entry into the ventricle, and proximity of the tumor to the ventricular system, on CSF tumor dissemination and survival. (14-21, 34, 37, 101, 105-114). Neither dissemination nor survival were found to be influenced either by ventricular entry during surgery or proximity of the tumor to the ventricular system. Survival rate was significantly decreased, however, once CSF tumor dissemination had occurred. (22-32, 34, 56, 77, 80, 90-101). LM can occur even in the absence of surgical intervention. In current neurosurgical practice, while it is recognized that entering various CSF compartments could potentially lead to seeding, it is not felt that such maneuvers have a clinically significant negative impact. Little data is available which directly pertains to the molecular mechanisms through which CNS tumors might gain access to, and disseminate through, the leptomeningeal space. Most of the current understanding is based on extrapolation from in vitro and in vivo studies of cultured glioblastoma cells. Malignant glioma cells are believed to be highly mobile, (18-20, 36, 39-56, 89, 100, 104, 113) in addition to being able to proliferate rapidly. They can secrete a variety of proteases including urokinase (also called urokinase-type plasminogen activator, or u-PA), matrix metalloproteinases, and/or lysosomal cysteine peptidases called cathepsins. (11, 21-25, 33, 58, 66) Such proteases facilitate the processes of migration and invasion by causing breakdown of the extracellular matrix and other physiologic microstructures within the CNS (14, 68, 95). Evidence also suggests that altered expression of certain membrane adhesion molecules (such as CD44 or cadherins) correlates with a tumor's ability to invade pial, arachnoid, ependymal, or even endothelial barriers. (14, 26, 28-33, 68, 95). Such phenotypic characteristics are likely to be important prerequisites for the metastatic process.

According to CNS tumor types leading to LM: children and adults, the high tendency for several types of childhood brain tumors to metastasize to the leptomeninges has long been recognized. In addition to medulloblastoma, these tumors include ependymoma, germinoma, pineoblastoma and other primitive neuroectodermal tumors (PNETs). (2-4, 11-15, 30, 31-33, 90-94, 104-111) The leptomeningeal spread of pediatric posterior fossa tumors has been especially well-documented. (13, 15-19, 30-37, 40-53, 60) The known propensity of these tumors to lead to "drop metastases", i.e. metastases to the spinal subarachnoid space, has resulted in standard protocols for CSF analysis, staging of the entire neuraxis with gadolinium enhanced MRI, and the administration of cranio-spinal irradiation. Leptomeningeal spread has been reported to occur with other pediatric brain tumors, including juvenile pilocytic astrocytomas, brainstem and other gliomas, and tumors of the choroid plexus. (14-15, 19, 25-30, 32-38, 48, 61-77, 90) CNS tumors that have been found to produce LM both in children and adults are listed in Table 1.

It should be noted that in Table 1 (see below), no particular order has been assigned and many of the tumor types listed are from single case reports, or very small series.

Table 1. Primary CNS Tumors Reported to Produce Leptomeningeal Metastases

Children	Adults
Medulloblastoma	Glioblastoma
Ependymoma (benign and malignant)	Grade III astrocytoma
Germ cell tumors	Germ cell tumors
Pineoblastoma	Ependymoma
Primitive neuroectodermal tumor (PNET)	PNET
Juvenile pilocytic astrocytoma	Oligodendroglioma
Brainstem glioma	Low-grade glioma
Pleomorphic xanthoastrocytoma	Craniopharyngioma
High-grade glioma (other)	Malignant (and clear cell) meningioma
Choroid plexus papilloma/carcinoma	Primary cerebral fibrosarcoma
Ganglioglioma	Pituitary adenoma
Polar spongioblastoma	Pineoblastoma
Spinal cord astrocytoma	PNET
	Central neurocytoma
	Dermoid/epidermoid
	Primary CNS lymphoma
	Meningeal hemangiopericytoma
	Primary diffuse leptomeningeal gliomatosis

For adults, review of the literature reveals reports of LM from both low and high grade primary CNS tumors of varying cell lineages. (1, 5-9, 46-49, 51-68) While the adult list is similar to that for children, the predominant histologies responsible for LM in adults are generally of higher grade, a reflection of the more frequent occurrence of these types of tumors in adults. More benign tumors more often have a longer interval between their initial diagnosis and the diagnosis of LM. Recurrent tumors and malignant tumors are generally more likely to be associated with LM. Spinal cord tumors have also been reported to lead to LM, including intracranial seeding, both in children and adults. (13-20, 69-72)

The incidence of LM from CNS tumors was recorded in series of pediatric and adult patients. The incidence of LM in children has ranged from 19% to 36%. (11, 15, 30, 32, 40-50, 70-78, 95, 111, 114) With respect to specific tumor types, in 1983 Tomita and McLone reported that five out of five patients with cerebellar medulloblastoma had neoplastic cells present in the CSF or arachnoid of the cisterna magna at the time of craniotomy before manipulation of the tumor. (37, 41-49, 69-83, 88, 101-108, 112) A more detailed study was then undertaken in which 31 children with medulloblastoma were studied by myelography and CSF cytology, one month after surgery, and prior to the administration of irradiation. Three patients (9.6%) showed results that were positive for spinal subarachnoid seeding. (34-42, 76, 82-92)

The incidence of leptomeningeal metastasis in patients with medulloblastoma is known to vary with the age of the patient, with younger patients having a higher incidence of LM at time of diagnosis. The likelihood of LM is also known to vary with stage of the disease, e.g. initial diagnosis vs. tumor recurrence. In studying children with low-grade gliomas, Civitello et al found LM in one of 56 cerebellar tumors, one of 34 cerebral tumors, one of 21 chiasmatic tumors, 0 of 14 diencephalic tumors, and three of 12 spinal cord tumors. (27-33, 40, 49, 55-62, 71-82, 91, 96) The incidence of LM in children with brainstem gliomas has been reported to range from 4 to 33%. (46, 62, 70, 109) Ependymomas, germ cell tumors and choroid plexus carcinomas are also known to frequently produce spinal seeding and/or "drop" metastases.

For adults, Awad et al. reported a LM incidence of 7% in a series of 191 patients with supratentorial malignant gliomas. (6-14) Erlich and Davis found that 25% of 25 patients with glioblastoma had spinal LM as discerned at autopsy. (61-69, 72-77, 92) In another autopsy study of glioblastoma patients, Onda and colleagues found that 14 of 51 patients (27%) had dissemination of tumor cells into the CSF. (74, 76, 85-88, 90) Clinical symptoms were found to be related to how extensive the seeding was. Wai-Kwan et al reported an incidence of 23% of LM in patients with malignant glioma as proven by autopsy. (67, 110-113) In a study by Elliott et al. (34), CSF dissemination could be radiographically documented in 35% of patients with malignant gliomas. Schild et al (97) reported leptomeningeal seeding in 10% of patients with benign ependymoma, and 41% in patients with malignant ependymoma. (33, 71, 78, 97) In addition to tumor type and grade, the incidence of LM in adults may depend upon additional factors such as age and the extent of tumor spread at time of diagnosis. In a recent study of 9672 patients of all ages having primary tumors of the brain or spinal cord, 11.5% had involvement of the cranial meninges and 2.2% had involvement of the CSF or spinal meninges. This study was based on patients collected through tumor registries; the diagnosis of meningeal and/or CSF involvement was made by clinical symptomatology and/or diagnostic imaging. (20-34, 75-83)

In contrast to studies cited above, Nishio and colleagues reported finding evidence for leptomeningeal seeding of the ventricular surface and/or subarachnoid space in 76.9% of the patients they studied. 16 Patients had a variety of primary CNS tumors, and were studied in detail at the time of autopsy. Malignant tumors showed tumor seeding more often than benign ones. In all of the cases in which seeding occurred, the primary tumor was found to extend directly into the CSF. The distribution of the tumor metastases correlated with CSF flow and the site of focal ependymal defects. Nishio et al. attributed their higher incidence to the fact that their patients were scrutinized more closely by detailed autopsy. The fact that there is such a wide range of reported incidence rates, both in children and adults, is a product of the fact that the patients studied, and methods used, have varied from study to study. Analysis of patients for the occurrence of LM on clinical grounds is also clouded by the sometimes rapid progression of the primary tumor, with patients succumbing to the disease before the diagnosis of dissemination can be made.

The diagnosis of LM in brain tumors in general can be difficult to make, since patients may initially have vague complaints and minimal neurologic findings. LM may go on to mimic other disorders, such as tuberculosis or fungal meningitis, CNS sarcoidosis or pseudotumor cerebri. (10, 31, 76, 83-90, 101) As mentioned previously, lymphomatous meningitis and PDLG, primary neoplastic diseases of the leptomeninges, would present a similar picture. The diagnosis of LM for brain tumor patients can also be hampered by the vagueness of the symptoms that may be present, especially since the CNS is already involved with tumor. Occasionally, patients with primary brain tumors exhibit features of LM at the time of their initial presentation. (31, 37, 39, 77, 99, 105-108) Multiple cranial nerve lesions as the initial manifestation of glioblastoma, for instance, is only rarely seen. (26, 77-89) Usually, for patients known to have a malignant brain tumor, there is little relevance to making the additional diagnosis of LM. This situation may change as treatment of the primary site improves. In patients for whom the diagnosis of LM has been important, such as pediatric medulloblastoma and ependymoma patients, more clinical research efforts have been focused. Symptoms and signs of LM may be secondary to CSF obstruction and hydrocephalus (headache), cranial nerve involvement, involvement of the region of the fourth ventricle (intractable vomiting), irritation/compression of spinal nerve roots or spinal cord, or irritation of the cerebral cortex (seizures). (5, 17-23, 38-41, 46-56, 60-68, 70-77, 82) The key to the diagnosis of LM in a CNS tumor patient often lies in detecting symptoms and signs related to nervous system involvement in a new location. A typical scenario would be a patient with a supratentorial tumor presenting with new lower cranial nerve findings, or a cervical or lumbar radiculopathy. The extent of meningeal spread may be quite advanced by the time the diagnosis of LM is made.

Table 2 (see below) shows a list of symptoms and signs that are possible in patients with LM; These findings may also be seen in patients with primary CNS tumors without LM

Table 2. Possible Symptoms and Signs of Patients with Leptomeningeal Metastases

Cranial	Headache	Nausea
	Seizure	Nuchal rigidity
	Mental status changes	Papilledema
	Diplopia	Dysphagia
	Other cranial nerve palsies	
	Weakness	
	Intractable vomiting	
	Hypothalamic dysfunction	
Spinal	Back pain	Radiculopathy
	Myelopathy	Paralysis
	Incontinence	

Diagnostic studies such as MRI or computerized tomography (CT), with and without contrast media, are usually indicated at intervals for any patient with a known primary CNS tumor. Findings indicative or suspicious for LM include enhancement along the pial and/or ependymal (periventricular) surface (especially in a nodular pattern), obliteration of sulci or other structures normally containing CSF (such as the basal cisterns), and/or the occurrence of hydrocephalus. While T1 imaging is standard, T2 imaging may also be helpful. It is anticipated that in the future, with the availability of clinical MRI units having even higher field strengths, even smaller metastatic deposits will be detected. Additional techniques, such as diffusion tensor imaging are also becoming available and may prove to be of value. The need for detailed imaging of the entire neuraxis, usually by MRI with and without gadolinium administration, depends on the patient's age, tumor type, clinical presentation and relevance of any positive findings. Proximity of the primary tumor to the ventricular system, other CSF pathways, or the pial surface of the brain or spinal cord would arouse suspicion for potential leptomeningeal seeding. Screening MRI scans of the entire spine are routinely performed for children with medulloblastoma, supratentorial PNET, ependymoma and germinoma. No such standards exist for adult patients with malignant gliomas. The reason for this seems to be the relatively low incidence of metastases and uncertain clinical significance of detecting LM in this population. As mentioned above, leptomeningeal dissemination may cause hydrocephalus, and treatment (usually with a ventriculoperitoneal [VP] shunt) may be needed. It has been hypothesized that communicating and/or noncommunicating hydrocephalus could be caused in LM patients by: 1) mechanical obstruction of CSF pathways, 2) blockage of the sites of resorption of spinal fluid by tumor cells, either over the cerebral convexities or in the spinal subarachnoid space, 3) alteration of CSF viscosity due to increased protein content, and/or 4) increased fibrinogen in the CSF with conversion into fibrin (and fibrosis) at the basal cisterns and/or Pachionian granulations. (27-29, 33-46, 66-80, 97-104, 110) VP shunt placement may risk further spread of tumor cells, but this may be unavoidable since increased intracranial pressure from hydrocephalus may be fatal. As with the clinical presentation of LM in general, CSF findings in patients with LM may be negative, or mimic those of other diseases. Standard CSF values in patients with LM from primary CNS tumors may be normal, or may show elevated protein, decreased glucose, increased cell number and/or positive malignant cells. (70, 74, 76, 90-95)

If the cell count is elevated, an increase in polymorphonuclear leukocytes may be seen. CSF cultures for fungus, and all other organisms would be expected to be negative. Performing a lumbar puncture in a patient with an intracranial mass lesion can certainly be hazardous; ventricular CSF may be available if the patient is requiring a VP shunt for hydrocephalus.

CSF cytology may be negative in patients with LM from CNS tumors, especially early in the clinical course. (29-31) In adults, studies attempting to correlate preoperative or postoperative CSF analysis with tumor diagnosis or degree of malignancy have not shown any reliable means for identifying those at risk for LM, (10-12, 14, 81).

Balhuizen et al found positive preoperative CSF cytology in 13.9% of their glioma patients, although there was no correlation for risk of postoperative LM. Sampling of CSF by lumbar puncture to document the presence or absence of malignant cells at the onset of treatment has been found to be of value in children. Positive CSF cytology has been shown to correlate with increased risk of gross LM and poorer overall prognosis. Negative CSF cytology, however, does not assure the absence of subsequent LM either in children or adults. (15-23, 30-35, 40, 56, 89, 93-99, 110-114). Regarding treatment and prognosis for LM in brain tumor patients, once the presence of LM from a brain tumor has been identified, options may include radiation therapy, systemic chemotherapy, and/or intra-thecal chemotherapy. Another option, especially for patients with leptomeningeal gliomatosis, is supportive care. (6, 12, 22, 31, 52, 67, 77, 110-114) Choice of treatment depends on which treatments have already been administered, and the age and clinical status of the patient. Steroids, usually dexamethasone, may be given, or the dose increased to ameliorate symptoms. Patients who develop hydrocephalus may need a ventricular shunt. Surgical intervention may be indicated at the site of tumor spread if a mass is present and prognosis is reasonable. Cases of drop metastases from CNS tumors (such as juvenile pilocytic astrocytomas and malignant meningiomas) have been treated with local surgical resection, especially when an isolated intra-dural metastasis has been present. (14, 19, 24, 33, 36-39, 48, 58, 79) Surgical resection has also been combined with spinal irradiation. Stereotactic radiosurgery has long been used to provide a precise high intensity boost of radiation in selected patients with recurrent intracranial tumors.

With the development of new devices having the capability of performing radiosurgery of the spine (such as the CyberKnife™), this technology might also be attempted for selected patients with drop metastases. Since the occurrence of LM in children with medulloblastomas, supratentorial PNETs, posterior fossa ependymomas, brainstem gliomas and germ cell tumors has been fairly well-defined, protocols for treatment with cranio-spinal radiation and/or chemotherapy have been developed. (4, 12-15, 26, 32-36, 43-46, 80)

The toxicities that are encountered may be quite significant. Often in the very young, every effort is made to attempt to avoid radiation therapy. Cranio-spinal radiation and/or chemotherapy have also been used to treat LM for more benign childhood tumors. (4, 36-47, 61, 79-90, 104) Controversies still exist concerning the indications for, and timing of, chemotherapy and radiation therapy in the pediatric age group. Follow-up measures for children with LM may include serial CSF analyses for cytology, and serial imaging studies, usually MRI with and without gadolinium administration. In adults with malignant CNS tumors, the occurrence of LM despite chemotherapy and/or radiation has usually been addressed with additional radiation treatments and/or chemotherapy. (46-49, 59-67) For LM from malignant glioma (intracranial or spinal), intrathecal chemotherapy with methotrexate, cytosine arabinoside (ara-C), thiotriethylenephosphoramidate (thio-TEPA), neocarzinostatin or ACNU has also been tried. (6, 53-62, 69-82, 89-99, 105) Of these choices, thio-TEPA may be the most promising.⁸² The potential toxic effect of intrathecal methotrexate administration is well known. (33, 56, 77, 83, 86, 99, 104) Adults are followed clinically for LM with serial neurologic examinations and MR imaging. For ventricular size, CT scanning is usually faster and less expensive than MRI. Follow-up CSF analysis is less likely to be of benefit in the adult population, and as mentioned above, lumbar puncture entails a risk of transtentorial herniation in the presence of supratentorial mass effect. The prognosis for children with LM is variable, and depends upon the patient's tumor type, age, and extent of the tumor's spread at the time of diagnosis. Disease may progress despite neuraxis radiotherapy and intensive chemotherapy, and systemic metastases may occur. (17, 31, 94-102, 104) In looking at pediatric patients with either medulloblastoma or PNET, Allen et al found the median survival for patients with LM at the time of diagnosis to be 12 months.³⁰ In a series review of 319 patients, Packer et al, found the median survival for patients, including all tumor types, to be six months. (15, 28, 77, 79-89, 93, 101-109)

Once there was evidence of relapse following treatment for LM, the median survival dropped to four months. When considering patients with the diagnosis of PNET, those with LM at the time of diagnosis fared worse than those without LM at the time of diagnosis, with an approximate five-year survival of 21% versus 54%.¹⁵ Civitello et al found the median survival for children diagnosed with low-grade gliomas and LM (combining all locations) to be only 25 months.⁴⁰ In looking at 14 patients with brainstem glioma and LM, Mantravadi et al found the five-year survival to be 28%.⁶² Unfortunately, the vast majority of adult patients with LM from primary CNS neoplasms have more aggressive tumor types and the prognosis is usually quite poor. Like children, prognosis may depend upon the type of the primary tumor, the age of the patient, and the extent of the tumor's spread.

Wai-Kwan et al found that for patients with high-grade gliomas, the median survival for those with LM at the time of diagnosis was 49 weeks. (67, 89, 103).

Awad et al reviewed 12 patients with high-grade glioma and LM at the time of diagnosis and found the average length of survival to be three months. (50, 53, 55-62, 80-84, 90) Better treatments for LM, including LM from CNS tumors, are certainly needed. (6, 34-44, 55-62, 71-84, 95-99, 101, 106)

The possibility of using immunotherapy for treating patients with LM has always been attractive. (29-31, 84, 90, 109-112, 114)

Coakham and Kemshead have reported on their experience with intrathecal administration of radiolabeled monoclonal antibodies. Of note is the fact that the best results were obtained in patients with PNET, where 53% of evaluable cases had responses or stable disease.

Nakagawa et al reported treating LM patients, including three having brain as the primary site, with continuous ventriculolumbar perfusion chemotherapy with some encouraging results. (86, 105, 110, 113-114) In their study, radioiodinated ventriculography was performed to confirm the absence of obstruction to CSF flow and intracranial pressure was carefully monitored. (11, 19, 37, 86, 113) Considering the difficulty in achieving therapeutic drug levels throughout the CSF space, further attempts at ventriculolumbar perfusion would seem to be warranted, especially if less toxic therapeutic agents can be identified. While reported relatively infrequently, LM from primary CNS tumors is a recognized and fairly well-described disease entity. Many primary CNS tumors, both malignant and benign, can lead to LM. In adults, the most common tumor to lead to LM is a high-grade glioma. Several types of pediatric brain tumors are well known to seed the neuraxis, especially medulloblastoma, ependymoma, PNET, brainstem glioma and germinoma.

While currently the incidence of LM can only be estimated, it seems that the more closely one looks, the more likely one is to find LM. Thus in the future, with improved, higher field strength MRI, it is likely that the diagnosis of LM will be made earlier and more often. Treatment for LM usually includes radiation therapy, and chemotherapy; selected surgical procedures may also be needed. Prognosis, while varying especially according to age and tumor type, is generally poor even with aggressive treatment. Ventriculolumbar perfusion therapy and intrathecal administration of radiolabeled monoclonal antibodies have been used experimentally in patients with some intriguing results.

Further information about the basic science of CNS tumor cell proliferation and metastasis is needed, and novel approaches to this disease should continue to be conceived, funded and tested (13, 18, 29, 56, 73, 110, 112-114).

Intramedullary metastases from high grade glioma and glioblastoma are uncommon (7, 10, 19-28, 33-41, 43-50, 58, 66-72) and may present with or without leptomeningeal metastases (11-12, 15-19, 33-40). Simultaneous leptomeningeal and intramedullary metastases from glioblastoma are very rare (9, 13-16, 19-26, 35-39, 42-50, 66-69). Intraspinal metastases from astrocytomas have been less commonly reported. The mechanism of metastatic spread is thought to be due to seeding of tumor cells via CSF pathways either from direct spread into the subarachnoid space or from iatrogenic spread following surgical manipulation.

Cytological changes in cerebrospinal fluid (CSF) associated with resections of intracranial neoplasms was reported by Robert H. Wilkins et al in the Journal of Neurosurgery in

July 1966 / Vol. 25 / No. 1 / Pages 24-34.

Erlich et al. (4-5, 16, 39-52) reported leptomeningeal metastasis in five out of 20 spinal cords of patients with GBM examined post-mortem, with one suffering clinical symptoms.

Awad et al.(5, 8, 19-27, 38, 44) conducted a retrospective review of patients with supratentorial high-grade gliomas and identified 13 out of 191 with unequivocal evidence of leptomeningeal metastases. Of these, eight patients had symptoms, but a firm diagnosis was only established pre-mortem in five cases.

Vertosick et al.,(6, 109, 112) in 1990, reported that 11 out of 600 (2 %) patients with intracranial GBM had symptomatic intraspinal dissemination and, in 1986, Choucair et al.(17, 26) diagnosed spinal cord metastases in five of 405 patients

(1.2 %) with GBM. In 1992, Schwanager et al.(7) summarised 22 cases from the literature along with one case of their own of symptomatic intraspinal metastases from GBM.

In 2001, Hubner et al.(8) included their own series along with other published articles to increase the number of reported cases of symptomatic intraspinal metastases to 36. More recently, Scoccianti et al.(16) and Alatakis et al.(12) published case reports of patients with symptomatic leptomeningeal and intramedullary metastases from a GBM. They reported and suggested an increase in the number of symptomatic intraspinal metastases being reported.

In another series, Stark et al.(9) reported three out of 267 (1.1 %) cases of GBM who developed intraspinal drop metastases.

In the study about “Ventricular entry during resection of malignant gliomas: Effect on intracranial cerebrospinal fluid tumor dissemination” by Paul Elliott et al. it was reported that the ventricular system was not infrequently entered during the course of maximum cytoreductive surgery for high-grade supratentorial gliomas. It was unclear if ventricular entry during surgery and/or proximity of the tumor to the ventricular system affects cerebrospinal fluid (CSF) tumor dissemination or the patients' overall survival rate. The authors retrospectively reviewed hospital records and neuroradiological studies of 51 patients operated on at the University of Washington between 1987 and 1991.

Inclusion in this study necessitated a pathological diagnosis of malignant glioma and the availability of preoperative and postoperative computerized tomography scans or magnetic resonance images. Patients were excluded from the study if they had radiographic evidence of ventricular entry or CSF tumor dissemination prior to referral to the authors' institution. The index operation was defined as the first operation at the University of Washington or (in those patients with ventricular entry) the operation in which the ventricle was entered. Patients were followed until time of death or, in the case of survivors, until February, 1992. The effect of both ventricular entry and the proximity of the tumor to the ventricular system on CSF tumor dissemination and survival rate was assessed using statistical survival methodology.

There was no significant difference in time from diagnosis to the index operation between groups compared (Mann-Whitney U-test, $p > 0.40$). Cerebrospinal fluid dissemination was radiographically documented in 18 patients (35%) following the index operation. This occurrence was not significantly influenced by either ventricular entry during surgery (Mantel-Cox test, $p = 0.13$), the proximity of the tumor to the ventricular system ($p = 0.63$), or these two variables combined ($p = 0.28$). Survival rate following the index operation was not significantly affected by ventricular entry ($p = 0.66$), proximity of the tumor to the ventricular system ($p = 0.61$), or these two variable considered in combination ($p = 0.44$). However, survival rate was significantly decreased once CSF tumor dissemination had occurred (Cox model, $p = 0.03$). (4-9, 14, 17-18, 20-32, 45, 58, 69, 79-85, 94-99, 104-110)

Glioblastoma (GBM) is the most common primary brain tumor. It is treated aggressively with maximum safe resection followed by irradiation and temozolomide. Although both the progress-free survival (PFS) and the overall survival (OS) are significantly prolonged, recurrence is inevitable for almost every patient.

Several studies have evaluated the pattern of recurrence of GBM after concomitant chemo-radiotherapy (CCRT) has become a standard treatment. Recent studies reported that temozolomide might have impacted the timing and distribution of recurrence.(15) With intense local control and longer survival, the pattern of recurrence of GBM may have changed from distant spread as rarity to a higher proportion.(3,6,15) Molecular markers such as O6 -methylguanine-DNA methyltransferase (MGMT) methylation not only contributed to the prolonged survival duration but also increased the proportion of distant metastasis.(3) Some authors even suggested that surgical manipulation including the extent of resection[6] or ventricular entry during surgery (10,17) could alter the pattern of recurrence. Cerebrospinal fluid (CSF) spread of GBM, an indication of terminal stage for patients, is also becoming another increasing thorny problem for clinicians in recent years because scarce effective options could be offered. (12, 18, 43, 54, 70)

Classification of recurrence CCRT has been a remarkable milestone for the management of GBM. These combined therapies can significantly lengthen the survival of the patients. However, recurrence is still inevitable. Although the highest tolerable dose of irradiation has already been prescribed to the tumor bulk and its adjacent tissue, (4, 14, 16, 25, 36) the majority of tumor recurrence remained local. There is still no unified classification for the pattern of recurrence, especially “non-local” recurrence. Previous studies usually categorized tumor spread by either dosimetric method or by the distance to the primary tumor bulk.

In this study, a radiological methodology was presented for patterns of recurrence. The accuracy in delineation of GBM is improved by utilization of MRI, especially by using T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, for their sensitivity in picking up non-enhancing infiltrative tissue. Moreover, T2 sequence has superiority in picking up signals suggesting edema, where it is believed to shelter scarce GBM cells.[11] It is recommended by the Radiation Therapy Oncology Group that gross tumor volume should be contoured with computed tomography plus either T2 or FLAIR sequence. Thus, using T2-weighted and FLAIR as reference for distinguishing local from non-local recurrence (new parenchymal lesion) are comprehensible and straightforward.

With the presented methodology, differentiation between CSF dissemination and parenchymal infiltration of GBM is also feasible. It is believed that the GBM cells would be able to spread freely and widely within the CSF space if they invaded basal membrane with implantation in the subependyma and choroid plexus. (7, 9, 16, 22, 30, 50-61, 100)

Direct invasion of ependymal and tumor fragmentation in contact with CSF are related to CSF dissemination. (12, 18, 23, 30, 34, 86-90) Given the information, it is alarming for a clinician to highly suspect CSF dissemination of disease upon detection of ependymal contrast enhancement on MRI. The reported incidence of CSF dissemination of GBM varies from 2 to 25%, (1, 10, 20, 39, 44, 57, 60, 71, 88-101, 111) whereas the symptomatic one was around 1.3 to 8.8% only. (16) A more recent review suggested that CSF spread has been increasing steadily over the past few years maybe because of the improvement of imaging modalities as well as prolonged survival. (18, 37, 89, 104)

The current best laboratory study for the diagnosis of CSF spread of malignancy is CSF cytology. While even for patients with genuine leptomeningeal metastasis, 55% of them will have initial false negative CSF cytological results, not mentioning the remaining chances of misdiagnosis still remains up to 14% after 3 lumbar punctures. This high false-negative rate is meaningful for clinical practice. Other abnormalities yield from CSF examinations such as elevated opening pressure or protein level are only suggestive instead of diagnostic. (5) Because CSF dissemination of GBM takes place in terminal stage of disease and the outcome is always dismal, (12-19, 30, 41-56, 78-90, 100, 111) with extremely shortened survival, many physicians are reluctant to administer invasive procedure with such a high false-negative rate.

More importantly, it was reported and demonstrated that the new lesions widely disseminated via CSF could grow within the irradiation high-dose zone. These tumors were usually labelled as central or in-field recurrence (local recurrence) by other studies. This would indicate that conventional dosimetric classification for pattern of recurrence suffered from the drawback of categorizing atypical recurrences. MGMT methylation: With the ongoing studies focusing on different aspects of the MGMT methylation status, MGMT methylation might also have some impacts on recurrence.

Brandes et al. showed that the incidence of distant recurrence for patients with methylated MGMT status was significantly higher than that for patients with non-methylated MGMT status, which were 42 and 15%, respectively. (3, 50, 56, 89-101, 111)

GBM cells with methylated promotor status are vulnerable to irradiation especially when given concurrently with temozolomide (Temodal). However, pharmacokinetic study suggested that the efficacious dose of temozolomide (Temodal) for eliminating GBM cells could not be reached within the CSF space. (2, 8) It is also fair to theorize that CCRT resulted in therapeutic pressure onto the lesion and might also simultaneously select GBM cells, which have the propensity to migrate and subsequently harbor in the CSF space. The above mentioned hypothesis could also explain the finding of 5 out of 11 patients who received temozolomide suffering from CSF dissemination with stable primary lesion in this study. Whether the ventricular entry during surgery could raise the incidence of CSF spread has remained controversial among studies for decades. (8, 10, 17, 44, 50) CSF could be contaminated with GBM cells after surgically breaching the ventricular lining. The vitality of dispersed GBM cells, no matter caused by contamination or being pre-existed, could be suppressed by immune reactions within the CSF space. While the current intensive treatments including irradiation and chemotherapy for GBM, in addition to bringing outstanding curative effect intracranially, they are suspected to be causative of compromised immune function, and thus favor those cells with ability and the time needed to propagate within CSF space (19). The matter of prolonged survival was discussed in the literature. Despite no statistical significance, patients suffered from CSF spread of disease who had perceived seemingly better disease control and held the shortest longevity after progression. Thus, early recognition of CSF spread is increasingly important. With improved local control of primary disease as well as survival, CSF spread of disease is becoming an arduous challenge that needs to

be tackled. As both the completion of CCRT and methylated MGMT promotor status in GBM are associated with prolonged patient survival, it is also very reasonable to speculate that these patients live long enough for this rarely seen but possible tumor behavior to occur. Literature suggests that the time for the CSF spread to be manifested ranged from 12–15 months post-surgery, (14,15, 18-32, 34-50, 59, 100) which was concordant with longer PFS for patients with MGMT methylated GBM as well as that for patients treated with CCRT in this study.

Similar findings were also present in some of the pattern of recurrence studies. (3, 15, 19, 24, 50, 59-63) With the prolonged stable phase, GBM could no longer be regarded simply as local but rather a neuroaxis disease.

Pattern of recurrence and factors associated with cerebrospinal fluid dissemination of glioblastoma was described in the so called Chinese study of 36 patients by Danny T. M. Chan et al. published in Surg Neurol Int. 2016; 7: 92. (See the following Tables 3-5, figure 9 and diagram 1)

This study showed that the incidence of CSF spread of GBM was prominent in Chinese population despite the majority of the recurrence still being located within the original tumor bed. Ventricular entry during excision of GBM should be avoided. Patients who are able to complete CCRT have a risk for CSF dissemination. GBM patients with methylated MGMT promotor status are prone to suffer from CSF dissemination recurrence. MRI for whole neuroaxis (brain and spine) should be considered, especially for patients with longer PFS.

Table 3: Patients, gender, EOR, Radiotherapy, Chemotherapy, MGMT examination of the Chinese study

Characteristics	Patients, n
Median age (range) year	52.5 (23-72)
Gender	
Male	26
Female	10
EOR	
Total resection	6
Subtotal resection	30
Concurrent TMZ with RT	
Yes	29
No	7
Concurrent TMZ	29
Completed	19
Incomplete	10
CCRT	19
Completed	10
Incomplete	9
MGMT	31
Methylated	14
Unmethylated	17

EOR denotes extent of resection, TMZ: Temozolomide, RT: Radiotherapy, CCRT: Concomitant chemoradiotherapy and MGMT O⁶-methylguanine-DNA methyltransferase

Table 4: Therapy overview of the patients in the Chinese study

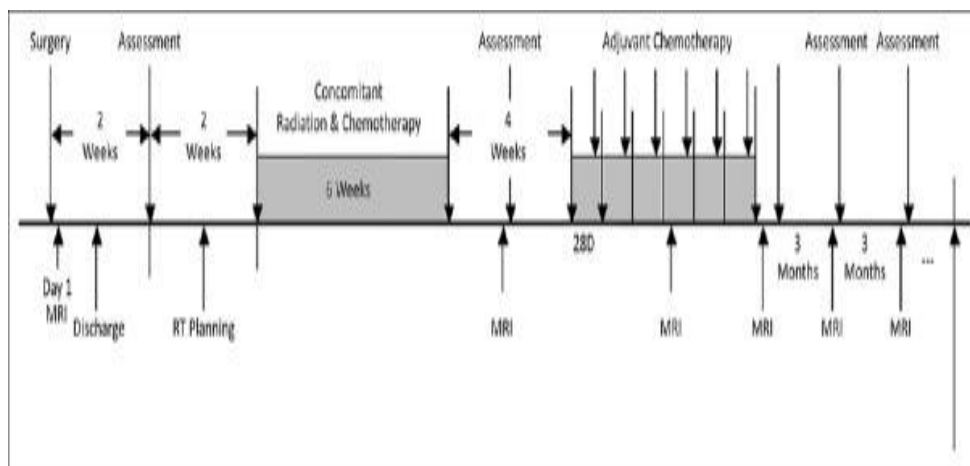


Table 5: Risk factors for the CSF dissemination and local / new recurrence and measurements of P values of the patients in the Chinese study

Risk factor	CSF Dissemination	Local + new parenchymal Recurrence	<i>P</i> value ^a (univariate)	<i>P</i> value (multivariate)
Age			0.924 ^b	
Extent of Resection				
Total Resection	2	4	0.609	
Subtotal Resection	9	21		
Ventricular Entry				
Yes	5	2	0.018	0.026
No	6	23		
MGMT				
Methylated	8	6	0.027	0.092
Unmethylated	3	14		
Corticosteroid therapy				
Yes	5	12	0.588	
No	6	13		
Concurrent TMZ				
Yes	10	19	0.291	
No	1	6		
CCRT				
Completed	6	4	0.046	0.027
Not completed	4	15		
Primary GBM				
Yes	10	22	0.644	
No	1	3		

CSF denotes cerebrospinal fluid, CCRT concomitant chemoradiotherapy, MGMT O⁶-methylguanine-DNA methyltransferase, TMZ temozolomide, GBM glioblastoma multiforme. a. Fischer's exact test, b. discriminant analysis *Italic and bolded fonts: Significant outcomes*

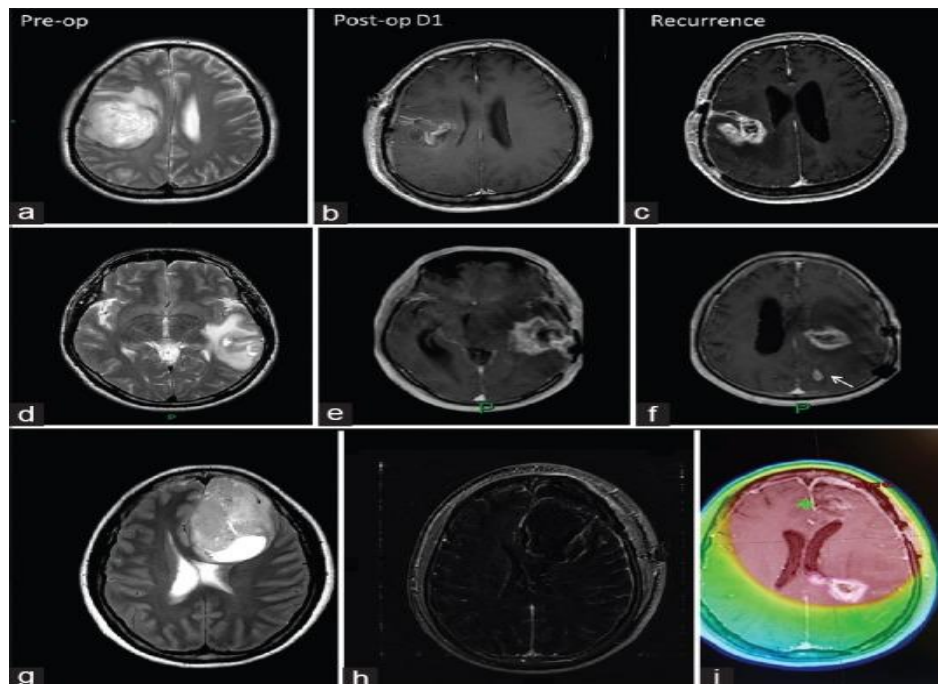


Figure 9: Illustrations for patterns of recurrence. (a-c) Local recurrence, (d-f) new parenchymal infiltration, (g-i) New CSF dissemination; (g) pre-operative MRI showing left frontal lobe GBM; 2h. MRI T1 + C fat subtraction suggested total resected lesion. (Chinese study).

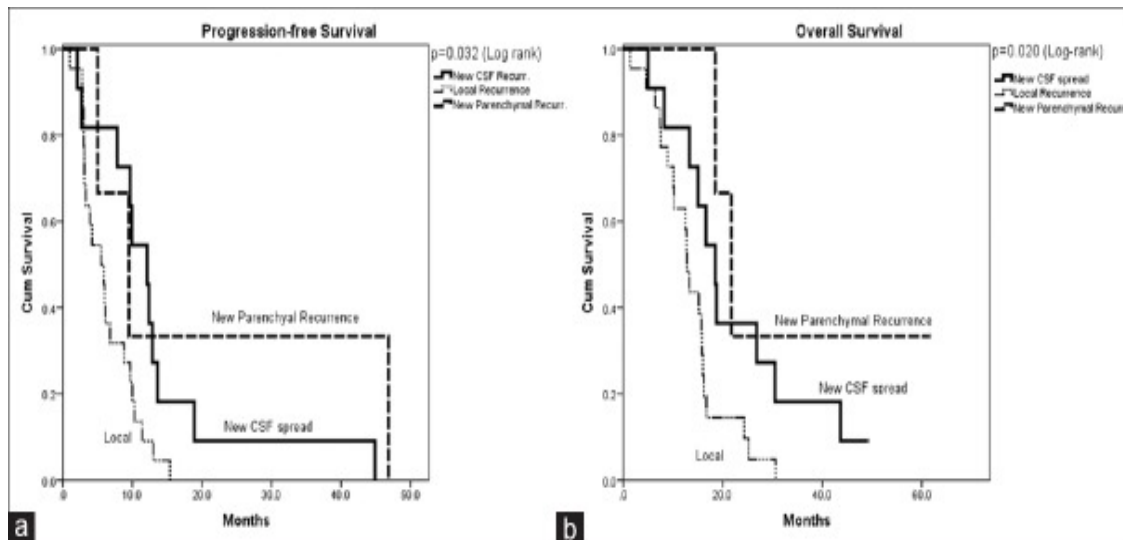


Diagram 1: Kaplan-Meier Survival Curve for 36 eligible patients in the Chinese study. (a) Progression free survival curves for 3 patterns of recurrence; (b) overall survival curves for 3 patterns of recurrence.

Glioblastoma Multiforme in the Pineal Region with Leptomeningeal Dissemination and lumbar metastasis was reported by Ryosuke Matsuda et al, Department of Neurosurgery, Nara Medical University, Kashihara, Japan. (4, 17, 24, 30-32, 42-46, 75-88, 93-94, 106-108).

Reported was a case of a 31-year-old woman with glioblastoma multiforme (GBM) in the pineal region with associated leptomeningeal dissemination and lumbar metastasis. The patient was presented with severe headache and vomiting. Magnetic resonance imaging (MRI) of the brain showed a heterogeneously enhanced tumor in the pineal region with obstructive hydrocephalus. After an urgent ventricular-peritoneal shunt, she was treated by subtotal resection and chemotherapy concomitant with radiotherapy. Two months after surgery, MRI showed no changes in the residual tumor but leptomeningeal dissemination surrounding the brainstem. One month later, she exhibited severe lumbago and bilateral leg pain. Thoracic-lumbar MRI showed drop like metastasis in the lumbar region. Finally she died five months after the initial diagnosis. Neurosurgeons should pay attention to GBM in the pineal region, not only as an important differential diagnosis among the pineal tumors, but due to the aggressive features of leptomeningeal dissemination and spinal metastasis.

GBM often occurs in the cerebral hemisphere, i.e., the frontal, temporal, and parietal lobes. But they are rare in the pineal region. Few cases of GBM in the pineal region have been reported (1, 4, 10-19, 24, 30-42, 46-75, 77, 84-94, 106-108). In this case report, the aim is to discuss the characteristics of GBM in the pineal region, and particularly the feature of spreading into the cerebro-spinal fluid space.

Reviewd and reported was a 31-year-old woman with no previous history presented with persistent severe headache and repeated vomiting at a local clinic. MRI of the head revealed a pineal tumor with obstructive hydrocephalus.

She was transferred to the hospital for further treatment. She underwent an urgent ventricular-peritoneal shunt. After the ventricular-peritoneal shunt, she improved dramatically. Subsequently, gadolinium enhanced-MRI of the brain showed heterogeneous enhancement in the pineal region without pituitary tumor and leptomeningeal and ventricular dissemination (Fig. 10). Blood examination showed normal serum levels of α -fetoprotein, β human chronic gonadotrophin and placental alkaline phosphatase. Cerebral angiography revealed a vascular rich tumor fed by the posterior choroidal artery and arterial-venous shunting. In order to confirm the pathological diagnosis and remove the tumor, she underwent subtotal resection of the pineal tumor with craniotomy using the occipital transtentorial approach. In the intraoperative findings, the tumor was soft and bled easily. It was easy to dissect the tumor from the splenium.

It was concluded that the tumor originated in the pineal region, not in the splenium or midbrain. Finally, subtotal resection was performed, because it was very difficult to stop the bleeding in the left superior and lateral parts of the tumor. Patient exhibited no new neurological deficits after the surgical resection.

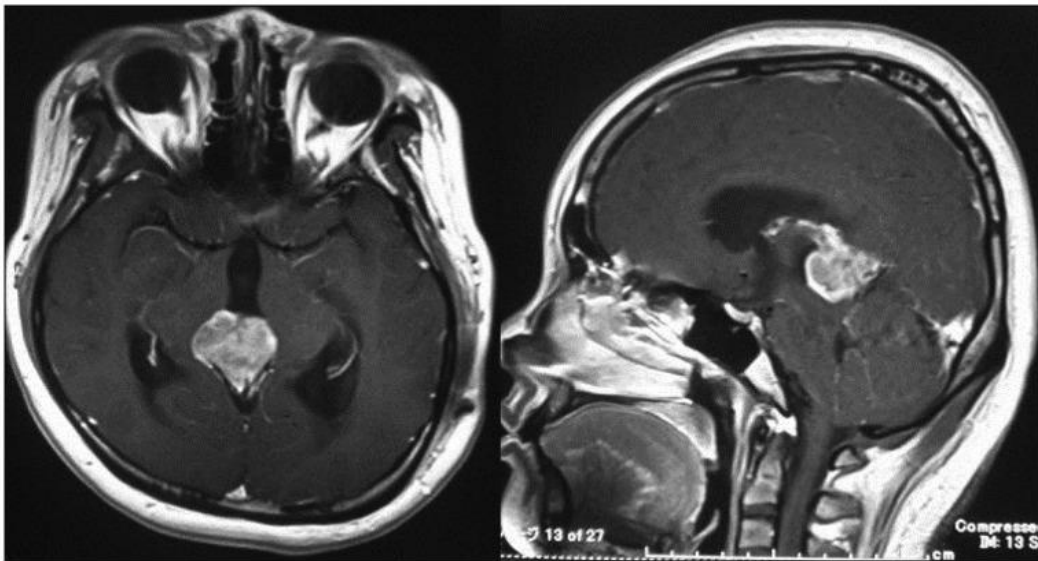


Fig. 10: Preoperative enhanced magnetic resonance images revealing a heterogenous enhancement of a pineal tumor with obstructive hydrocephalus.

Histopathological findings showed the feature of glioblastoma composed of poorly differentiated pleomorphic tumor cells with marked nuclear atypia and brisk mitotic activity (Fig. 11). Focal necrosis with pseudopalisading was found, and MIB-1 proliferation index was high (43.7%). Immunohistochemistry showed a positive reaction to the glial fibrillary acidic protein, S-100, nestin, and INI-1. On the other hand, it showed a negative reaction to synaptophysin and NFP-MH. After surgical resection, she was treated by radiotherapy with 60 Gy and daily administration temozolomide (75 mg/m²) for forty-two days. Two months later, postoperative MRI showed no change of the residual tumor but leptomeningeal dissemination surrounding the brain stem and upper cervical spinal cord (Fig. 12). She continued with temozolomide chemotherapy.

Three months after surgery, she experienced severe lumbago and bilateral leg pain. Thoracico-lumbar MRI showed drop metastasis (Fig. 13). She and her family refused any additional treatment, and finally she died five months after the initial diagnosis.

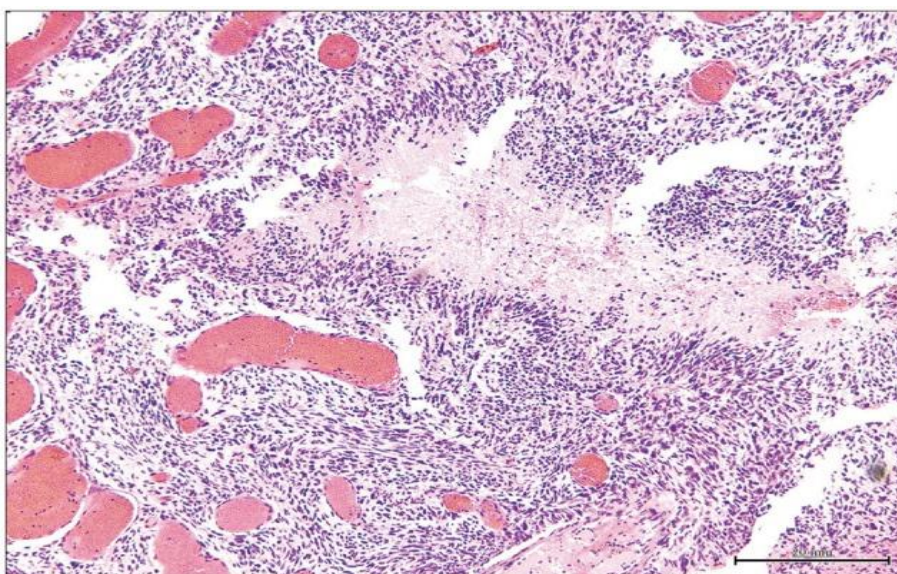


Fig. 11: Histopathological findings showing the feature of glioblastoma composed of poorly differentiated pleomorphic tumor cells with marked nuclear atypia and brisk mitotic activity and focal necrosis with pseudopalisading (H&E stain ×50).

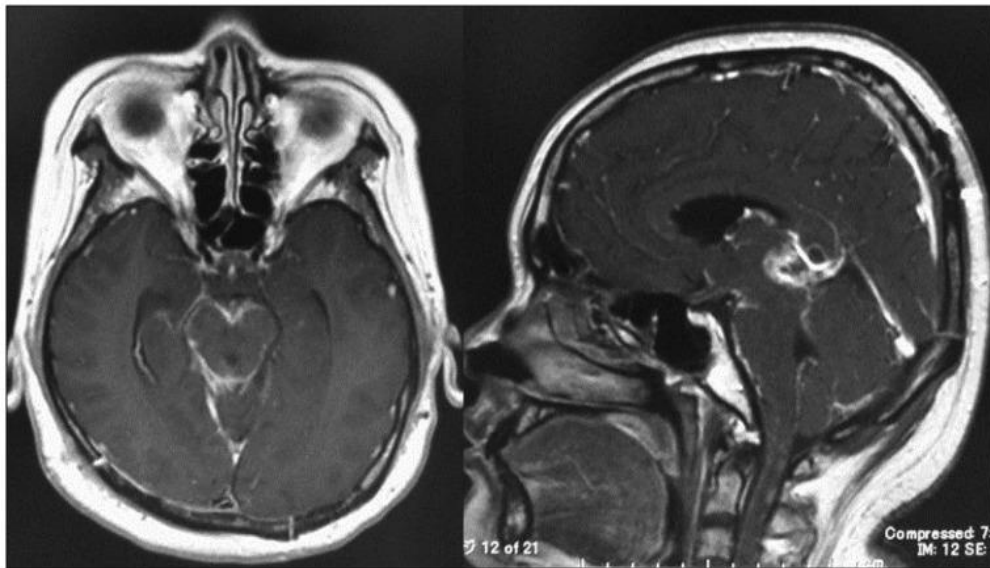


Fig. 12: Postoperative enhanced magnetic resonance images revealing an enhancement surrounding the brainstem and the residual tumor in the pineal region after radiotherapy concomitant chemotherapy.

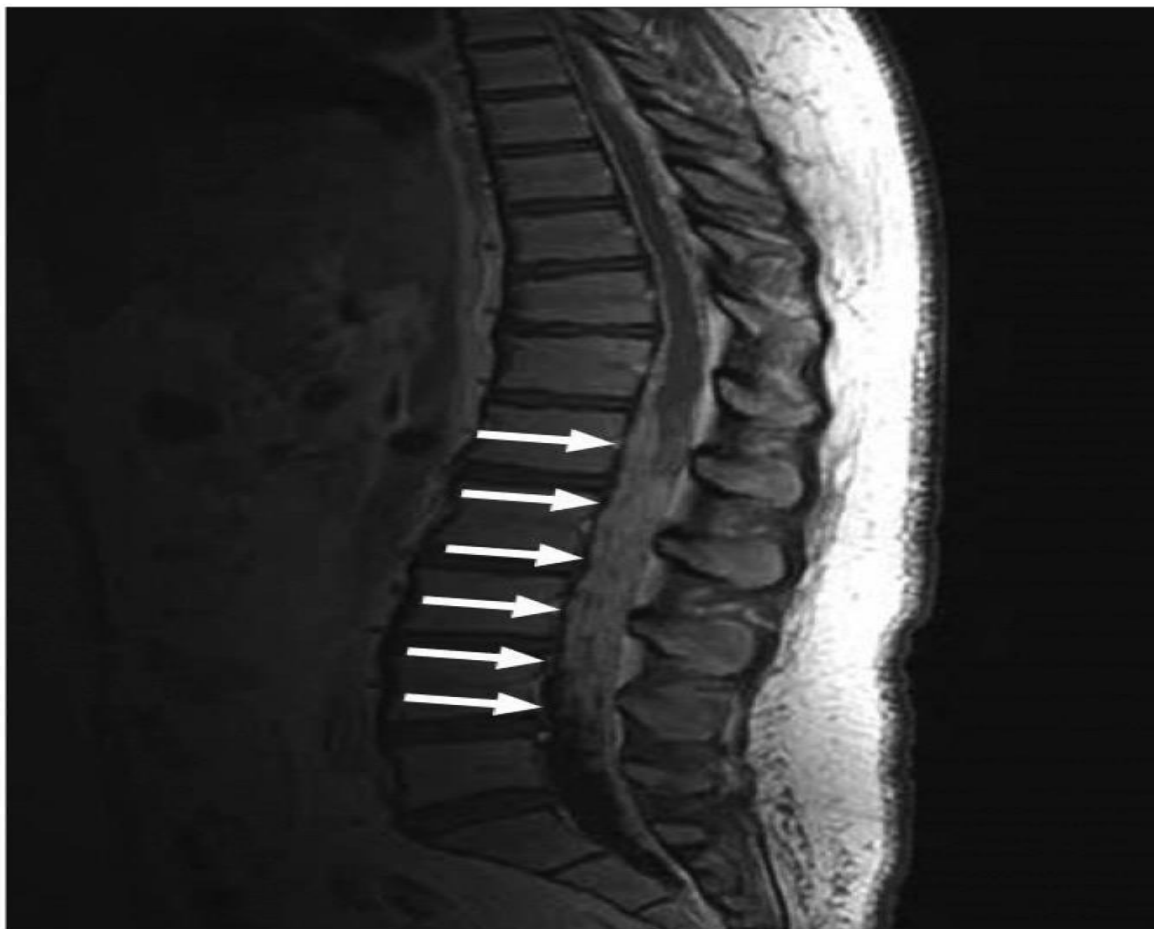


Fig. 13: Thoraco-lumbo-sacral enhanced magnetic resonance images revealing spinal metastasis in the lumbar region (white arrows)

GBM is categorized as grade 4 in the WHO scale, and is the most common malignant tumor in the brain, and often occurs in the cerebral hemisphere in adults (21, 93-99). On the other hand, the pineal region is a rare location for GBM. GBM in

the pineal region was reported for the first time in 1954 by Ringertz et al. (15, 93-95, 99). Since then, to the knowledge in general, only eighteen cases of GBM in the pineal region have been reported. (1, 23, 45, 78-89, 101-111, 113-114). The presenting symptoms of GBM in the pineal region are related to obstructive hydrocephalus, such as headache, nausea and vomiting, visual disturbance. Indeed, in many of the reported cases, including this case, ventricular-peritoneal shunts were required. Secondly, the symptoms are related to the direct compression to the midbrain, i.e., Parinaud's palsy.

A summary of glioblastoma multiforme in the pineal region is presented in the Table 6. Among the nineteen cases of pineal GBM reported previously including this patient, eleven patients were women and seven were men. The mean age was 42.5 years old (from 5 to 68 years). While twelve out of all cases were mentioned concerning the leptomeningeal dissemination, nine (75%) of them exhibited leptomeningeal dissemination upon autopsy or radiological findings using computed tomography (CT) and MRI. Concerning the spinal metastasis, four cases (25%) exhibited spinal metastasis; in the lumbosacral region in two, in the lower cervical and upper thoracic region in one, in the diffuse leptomeningeal carcinomatosis in one. In this review of GBMs in the pineal region, four spinal metastases (25%) developed out of eleven cases of pineal GBM. On the other hand, among the common GBMs, only 1.1% of all GBMs developed spinal metastases¹⁶). Symptomatic spinal metastases from GBM are rarely reported because most patients would not survive for the long time⁹). Furthermore, the interval between the diagnosis of the spinal metastasis and death was 2 to 3 months (4-7, 9, 17, 20-24, 29, 30-32, 37-46, 75, 84-88, 93-94, 106).

This insight suggested that the site of pineal region may play an important role in the development of spinal GBM metastasis and in the poor prognosis of pineal GBM.

Table 6: Summary of diagnosed glioblastoma multiforme tumors in the pineal region

No./Author (years)	Age/Sex	Pathology	Leptomeningeal dissemination	Spinal metastasis	Treatment	Survival time
1. Ringertz et al. ¹⁵ (1954)		GBM	NA	NA	NA	NA
2. Bradfield and Perez ³ (1972)		MG	NA	NA	Resection	0 M*
3. Bradfield and Perez ³ (1972)		MG	NA	NA	Shunt	27 M
4. Kalyanaraman ¹⁰ (1979)		GBM	NA	NA	Resection, RT	4 M
5. Norbut and Mendelow ¹² (1981)		GBM	Yes	Yes	Shunt, RT, spinal RT	4 M
6. Frank et al. ⁷ (1985)		GBM	NA	NA	Stereotactic biopsy, ¹²⁵ I implantation	4 M
7. Edwards et al. ⁵ (1998)		GBM	NA	NA	Resection, RT, chemo	18 M
8. Vasquero et al. ¹⁹ (1990)		GBM	No	No	Shunt, resection, RT,	6 M
9. Pople et al. ¹⁴ (1993)		MG	Yes	No	Shunt, resection, RT, chemo	4 M
10. Cho et al. ⁴ (1998)		GBM	NA	NA	Resection, RT	6 M
11. Gasparetto et al. ⁸ (2003)		GBM	No	No	Shunt, resection	2 M
12. Toyooka et al. ¹⁸ (2005)		GBM	Yes	No	Shunt, resection, RT chemo	11 M
13. Amini et al. ¹ (2006)		GBM	Yes	No	TVB, resection, shunt, RT, chemo	5 M
14. Amini et al. ¹ (2006)		GBM	Yes	No	TVB, resection, RT, chemo	7 M
15. Amini et al. ¹ (2006)		GBM	Yes	Yes	TVB, RT	2 M
16. Moon et al. ¹¹ (2008)		GBM	Yes	No	Resection, shunt	2 M
17. Birbilis et al. ² (2010)		GBM	Yes	Yes	Biopsy, shunt, RT, chemo	40 M
18. Ozgural et al. ¹³ (2013)	60/M	GBM	No	No	Shunt, biopsy, RT, chemo	24 M
19. Our case (2014)	31/F	GBM	Yes	Yes	Shunt, resection, RT, chemo	5 M

*Postoperative death. GBM : glioblastoma multiforme, MG : malignant glioma, NA : not available, RT : radiotherapy, Chemo : chemotherapy, WBRT : whole brain radiotherapy, TVB : third ventriculostomy and biopsy.

It remains controversial as to precisely when the spinal metastasis occurs. Birbilis et al. (2, 15, 18, 39-45) pointed out the potential for increased spinal spread of tumor cells during craniotomy. On the other hand, Elliot et al. (6) reported that the entry into the ventricle during the craniotomy did not significantly influence either CSF tumor dissemination or survival time in the supratentorial GBM.

While the mechanism of spinal metastasis, at least, remains controversial, the location of GBM, including the pineal region, intraventricular region, and adjacent to the ventricle, appears to be an important factor of the dissemination to the CSF.

The review of GBMs located in the pineal region indicated the poor prognosis and tendency for metastasis to the CSF, compared with common GBM. Neurosurgeons should pay attention to GBMs in the pineal region, not only as an important differential diagnosis among the pineal tumors, but due to the aggressive features of leptomeningeal dissemination and spinal metastasis.

Malignant astrocytomas of the spinal cord were reported and reviewed (4, 17, 24-30, 32-59, 75-88, 93-106, 108) by Alan R. Cohen and Fred Epstein in Journal of Neurosurgery, January 1989 / Vol. 70 / No. 1 : Pages 50-54. The authors reviewed their experience with the operative management of 19 consecutive cases of malignant astrocytoma of the spinal cord. There was a male to female ratio of 1.1:1, and the median age of the population was 14 years (range 1 to 32 years). The median duration of symptoms prior to definitive diagnosis was 7 weeks. Radical excision was carried out in all cases, with 18 patients (95%) receiving radiotherapy and 10 patients (53%) receiving chemotherapy as well. To date, 15 (79%) of the 19 patients in this series have died, with a median survival period of 6 months following surgery. No patient improved after operation. Hydrocephalus was present in 11 patients (58%), seven of whom underwent ventricular shunting procedures.

Dissemination of disease was found in 11 patients (58%). Extraneural metastases did not occur in the absence of a ventricular shunt. The authors concluded that malignant astrocytomas of the spinal cord are heralded by a short history followed by rapid neurological deterioration and usually death.

The rationale for operation is discussed, and an aggressive approach utilizing adjuvant therapy directed at the entire neuro-axis was suggested.

(See below mechanisms of leptomeningeal dissemination in diagram 2 and figures 14 and 15).

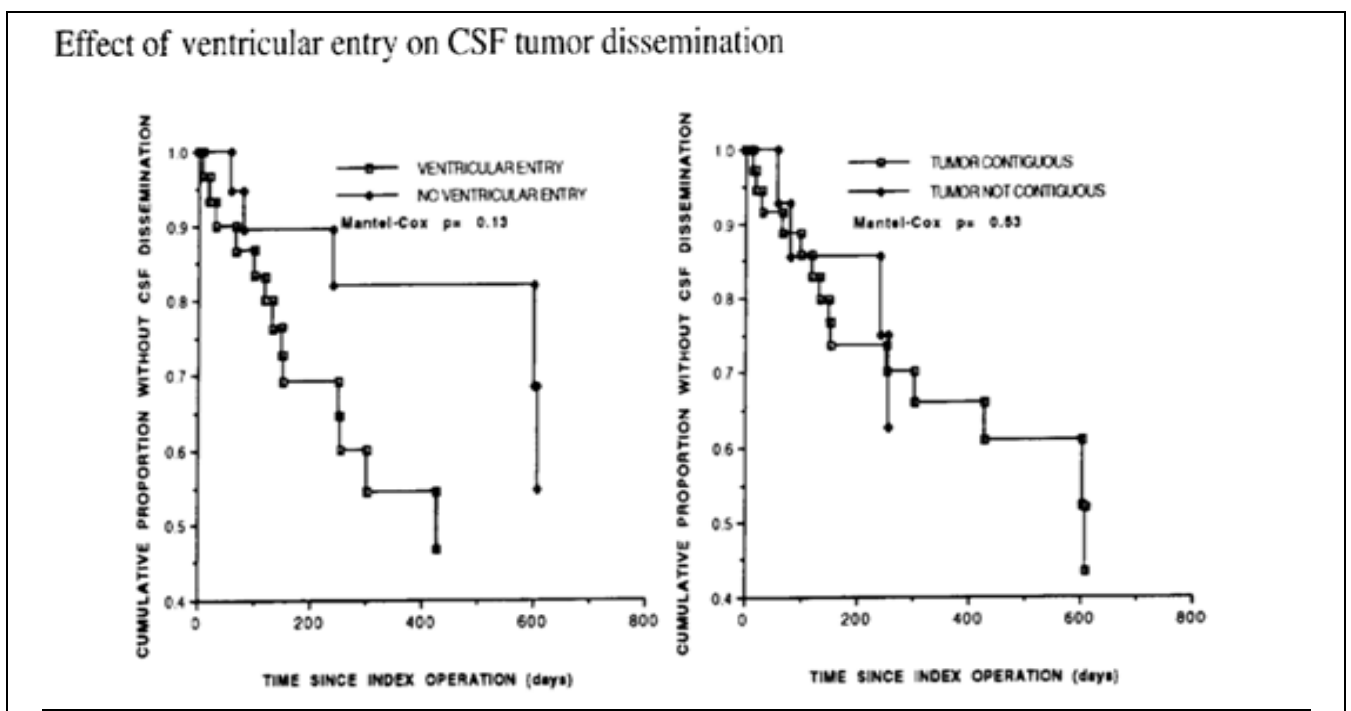


Diagram 2: Effect of ventricular entry on CSF tumor dissemination

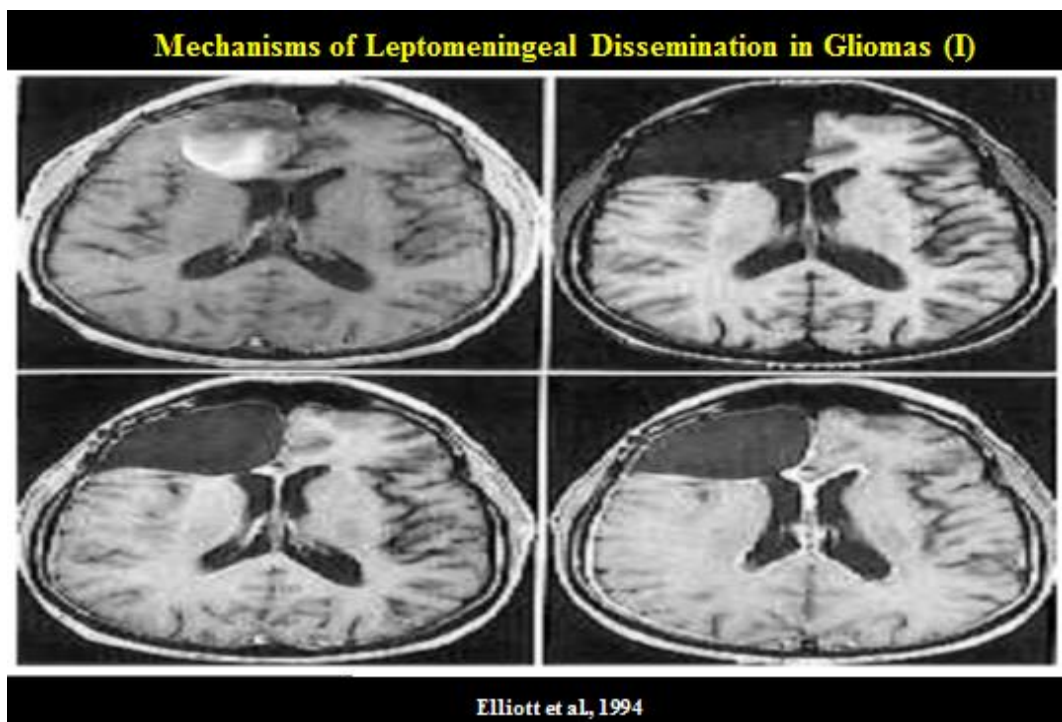


Figure 14: Mechanisms of leptomeningeal dissemination in gliomas (I)

Typically, intraspinal metastases occur in the lower thoracic, lumbar and lumbosacral spine possibly due to gravitational effects. The most common symptoms of leptomeningeal metastases are back pain, radicular pain in the limbs, paraesthesiae and other sensory symptoms followed by motor weakness (12, 15) and symptoms often progress rapidly.

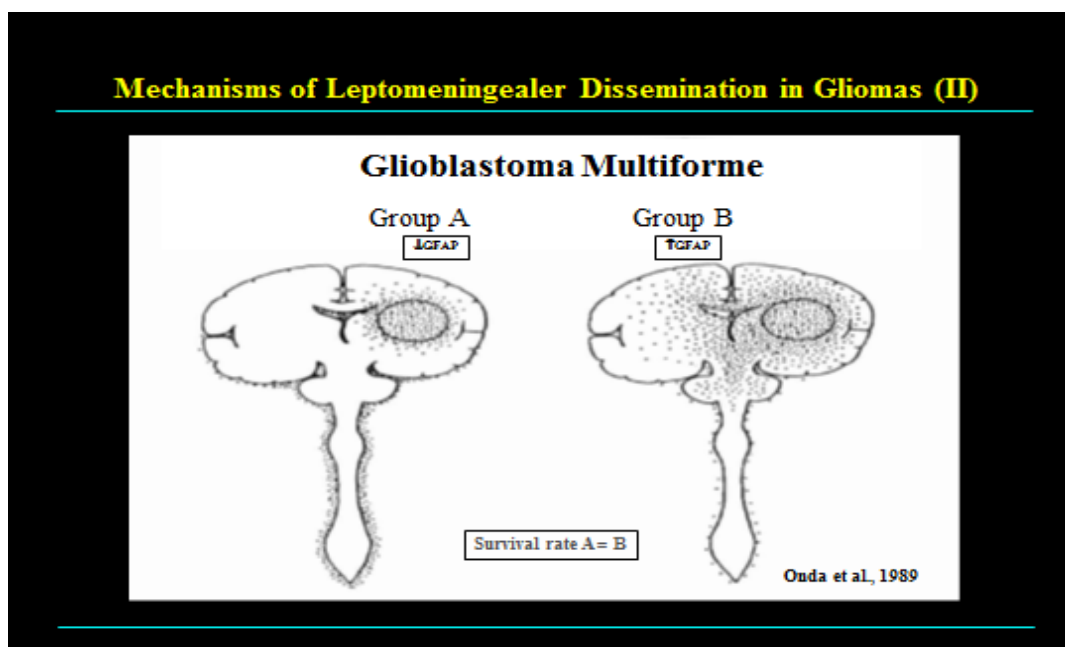


Figure 15: Mechanisms of leptomeningeal dissemination in gliomas (II)

Radiotherapy remains the most commonly used treatment modality, having demonstrated good symptomatic benefit. Varying total doses and dose per fraction have been reported with total doses of 20–40 Gy reported, (12, 15, 16, 97, 102-105) with most authors recommending hypofractionated radiotherapy with 2.5–4 Gy per fraction. (11-12, 18, 58-69, 89, 109) Radiotherapy to the spine has potential acute side effects (see Table 7).

Table 7: Toxicity of the radiotherapy to the spine

Effect	Management
Acute	
Tiredness	Advice about fatigue (e.g. moderate exercise, goal setting)
Initial flare of pain	Analgesia
Skin reaction	Aqueous cream
Diarrhoea	Loperamide
Nausea and vomiting	Antiemetics
Myelosuppression	Monitor full blood count (FBC), blood transfusion
Late	
Spinal cord damage	Warn patient
Ovarian failure	Avoid ovaries when planning treatment

Discussion of the cases in this study: Overall, the outcome in cases of leptomeningeal and intramedullary metastases is very poor, independent of treatment modality used, with median time between diagnosis of intraspinal dissemination and death previously reported as two to four months (6, 7, 12, 15, 16).

While surgery to the primary tumor is thought to increase the risk of drop metastases and each case in our series underwent surgery, drop metastases have also been reported in people who have not had any single surgery (2, 19, 33, 65, 70, 74-79, 83, 91, 94-99).

Patients in the present study were treated accordingly in varying fraction sizes from 1.8 to 4.4 Gy per fraction. Good initial palliation of pain was observed in each of the cases in this series, but improvement in neurological deficits was observed less consistently. In the present study, along with the reported literature, the radiotherapy reasonably well tolerated. Late side effects of this treatment are less relevant in this patient group as prognosis is so poor.

In the presented cases of this series, median survival following diagnosis of metastasis was one month (range zero to three months).

Back pain associated with leg weakness was observed in each of the cases in the present study while radicular pain, sensory symptoms and urinary retention were also seen.

Treatment of drop metastases is solely palliative and can include neurosurgery, radiotherapy, chemotherapy or steroid therapy.

However, given the overall poor prognosis of these patients, along with the fact that even apparently localized disease is highly likely to have further areas of spinal microscopic involvement, surgical management is rarely suitable in these patients.

4. CONCLUSIONS

Patients with malignant brain tumor, such as glioma / glioblastoma, presenting with complaints in the spinal region and / or associated spinal neurological signs or symptoms should raise the possibility of leptomeningeal and/or intramedullary spinal metastases. It is likely, that with improved diagnostics the number of symptomatic metastases detected will increase. This may have a corresponding therapeutic implication, with further attention paid to the use of chemotherapeutic strategies to attempt the reduction of the frequency regarding the intraspinal metastases. The importance of the awareness and recognition of this entity will therefore increase, especially as local control of primary malignant glioma is improving and corresponding clinical improvements in outcome and prognosis of this disease are observed. Consideration should be given to the symptomatic spinal radiotherapy, along with possible operative intervention for the spinal lesion, which can provide timely and effectively palliation of pain and possible improvement in neurological function.

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