AIM OF THE WORK

To review the radiosurgical management of brain metastases using Gamma Knife and to evaluate efficacy (local control of the lesion), survival longevity and quality (overall, neurological and new lesions free survival).

INTRODUCTION

Cerebral metastases is the most common malignancy affecting the brain . The 3 most common sites of the primary tumor are the lung, breast and gastrointestinal tract. Seventy persent of the patients with cerebral metastases have 1 or 2 lesions and 80% are located in the cerebral hemispheres.[1]

High dose corticosteroids are used for the initial treatment of patients with symptomatic brain metastases in order to decrease the edema that typically surrounds these tumors and to help restore neurological function.[2]

Systemic chemotherapy is not very effective against the most common types of primary tumors send metastases to brain ,whiche tend to be chemoresistant ,however it appears to be useful as an adjunct to other therapies for metastases from small cell lung tumors.[3]

The major weapons in the clinician´s arsenal against brain metastases include whole brain radiation therapy, surgical resection by open craniotomy and stereotactic radiosurgery.[4]

For the past 40 years, radiation therapy has played a major role in the palliation of metastases. In 1954 Chao and coworkers were the first to report the use of WBRT for the treatment of brain metastases.[5]

Effects of WBRT include mild fatigue, reversible hair loss, mild scalp erythema, hyperpigmentation and somnolence syndrome(persistent fatigue, anorexia and irritability especially in children.[6]

In long term survivors with metastatic brain tumor, long term toxicities associated with WBRT become apparent, progressive dementia, ataxia and urinary incontinence within 5 to 36 months of treatment with WBRT.[7]

Steriotactic radiosurgery uses sophisticated computerized imaging to precisely target a narrow radiation beam. Using this method, is possible to effectively destroy small tumors or close down abnormal blood vessels.7

This technique, which is accurate to one millimeter or less, does not require surgey and can be done on an outpatient basis. Radiation can be delivered using either the framed or frameless systems.7

Lars Leksell introduced the concept of stereotactic radiosurgery in 1951.The term is now applied to any technique that delivers a single high dose of ionizing radiation from an external source to a stereotactically defined intracranial target, ensuring a steep radiation fall off beyond the limits of the lesion.8

Steriotactic radiosurgery aims at irradiating precisely, in a single short treatment, one or several intracerebral lesions to stop growth of tumor s, to induce changes in blood vessels in the brain or alter function.8

Clearly there are benefits to both conventional surgery and RS. The advantages of surgery include immediate resolution of mass effect, pathological diagnosis and no risk of radiation necrosis.8

The advantages of RS include decrease risk of hemorrhage and infection and no risk of tumor seeding. RS also is less invasive and requires shorter hospital stays than standard craniotomy.9

RS has been shown to ameliorate symptoms even with tumors resistant to conventional radiation , such as melanoma, disadvantages of RS include potential exacerbation of peritumoral edema a requirement for long term steroid therapy and radiation necrosis.3

Appropriate treatment of metastatic brain tumors necessitates the judicious application of modalities such as open craniotomy, WBRT and SR. To afford patients the best opportunity for palliation and extended survival it is necessary to have affirm grasp of how these modalities best complement one another and to apply them accordingly.10

INTRACRANIAL METASTASES

EPIDEMIOLOGIC FEATURES:-

Metastatic brain tumors are the most common intracranial neoplasm in adults and are a significant cause of morbidity and mortality. Between 20% and 40% of all patients with metastatic cancer will have brain metastases at autopsy.[11]

The estimate of the incidence rate of metastatic brain tumors varies from 8.3-11 per 100,000. In two large population cohorts of patients who were diagnosed with colorectal, lung, breast or kidney carcinoma or melanoma, brain metastases were diagnosed in 8.5-9.6% of patients.The incidence varied by primary tumor site. The cumulative incidence was estimated at 16.3-19.9% in patients with lung carcinoma, 6.5—9.8% in patients with renal carcinoma, 6.9—7.4% in patients with melanoma, 5.0-5.1% in patients with breast carcinoma, and 1.2-1.8% in patients with colorectal carcinoma.[12]

The majority of patients who develop brain metastases have a known primary cancer (metachronous presentation). No primary systemic site of cancer is detected in 5—10% of patients with brain metastases. Patients with a history of lung cancer have the shortest latency period between the time of initial diagnosis and the diagnosis of brain metastases (median, 6-9 months). For renal cell carcinoma, the interval is approximately one year. Patients with breast, melanoma and colon cancer experience spread of their disease to the brain at a median latency of approximately two years.[13]

The detection rate of brain metastases appears to be increasing. This increase has been variably attributed to improvements in systemic therapy leading to longer survival, an aging patient population, and the ability of magnetic resonance imaging (MRI) to detect small metastases.
The majority of brain metastases are multiple, although the reported percentage of patients with solitary or multiple lesions may vary with the imaging modality used to make the diagnosis.[14]

In the CT (computed tomography) era 50% of lesions were thought to be solitary at the time of neurologic diagnosis.In an analysis of the Radiation Therapy Oncology Group (RTOG) database of brain metastases patients, 19% of patients presented with a single brain metastasis on MRI, and 50% of patients had 1—3 brain metastases. Melanoma has the greatest tendency to produce multiple lesions (75% of patients). Multiple lesions are also frequent in metastases from colon, breast and lung cancer. Renal cell metastases are more likely to be single.[15]

SEX:-

Predilection for gender follows that of the primary tumor. Lung cancer is the most common source of metastases in male patients, while breast cancer is the most common source in female patients. As the frequency of lung cancer in women increases, it may become the most common primary tumor to metastasize to the brain in women as well.[16]

AGE:-

Incidence of brain metastases based on age parallels that of primary systemic tumors. Brain metastases are most common in the fifth to seventh decades of life. Sarcomas and germ cell tumors are the most common solid tumors to metastasize to the brain in children.[17]

Patients with intracranial metastases far outnumber those who suffer from primary intracranial tumors. The diagnosis of a brain metastasis may be difficult for several reasons.

(1) Metastases can affect any central nervous system (C.N.S) location, mimicking both clinical and imaging findings of Primary intracranial tumors (Fig.1).

(2) Metastases are increasing in frequency as the first site of relapse in patients whose cancers have apparently been cured or are under good systemic control.

(3) Symptoms and signs of brain metastases may appear before the primary tumor has been discovered. In some instances, a patient may suffer multiple symptomatic intracranial metastases but the primary cancer is never found even after an extensive search.

(4) Primary brain tumors are more common in patients who have suffered other cancers than they are in the general population; Examples include meningiomas in patients with breast cancer.

(5) Other C.N.S processes, such as brain abscesses, can mimic brain metastases and occur with increased frequency in patients with cancer. Radiographic images often do not differentiate metastases from infection and diagnosis must be based upon the clinical situation and occasionally requires biopsy.

For all these reasons, diagnoses other than metastases must be considered in cancer patients who develop intracranial mass lesions and conversely, metastases must be considered in patients without known cancer who develop intracranial mass lesions.[18]

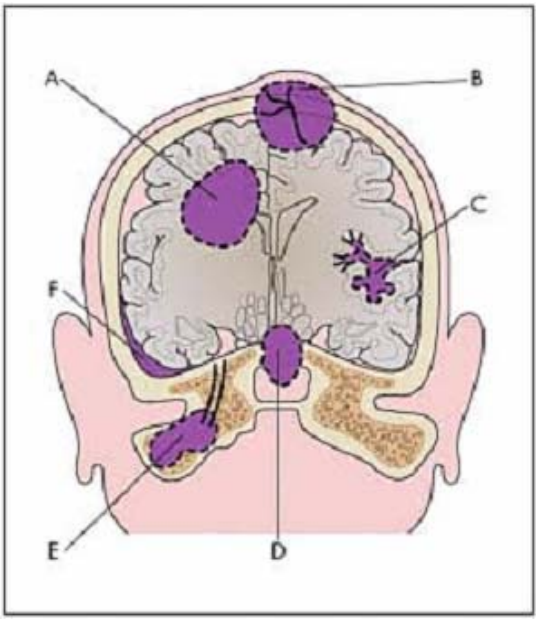

Figure 1

Cranial metastases. Most metastases affect the brain directly by hematogenous spread to the white matter of the cerebral hemispheres (A). The brain may be affected secondarily by a skill metastasis that invades the epidural space and compresses the brain. The skull metastasis may also compress the sagittal sinus (B) The tumor may involve the cranial leptomeninges and invade the brain by growing down the Virchow-Robin spaces (C) A metastasis to the base of the skull (D) or cranial nerves.[19]

PATHOPHYSIOLOGY OF THE METASTATIC PROCESS

To reach the brain, a tumor that arises elsewhere in the body must undergo complicated steps. This is so difficult that only a small number of tumor cells ever complete the process illustrated in (Fig.2). A systemic cancer begins in the body by a series of genetic steps not dissimilar from those that occur in primary brain tumors. Once established, the tumor grows, develops its own blood supply (angiogenesis) invades local tissues and enters the circulation by invading venules or lymph channels that eventually reach the venous circulation.[20]

Because systemic tumors enter the venous circulation and ultimately the right side of the heart, the first capillary bed they encounter is in the lung.[6]

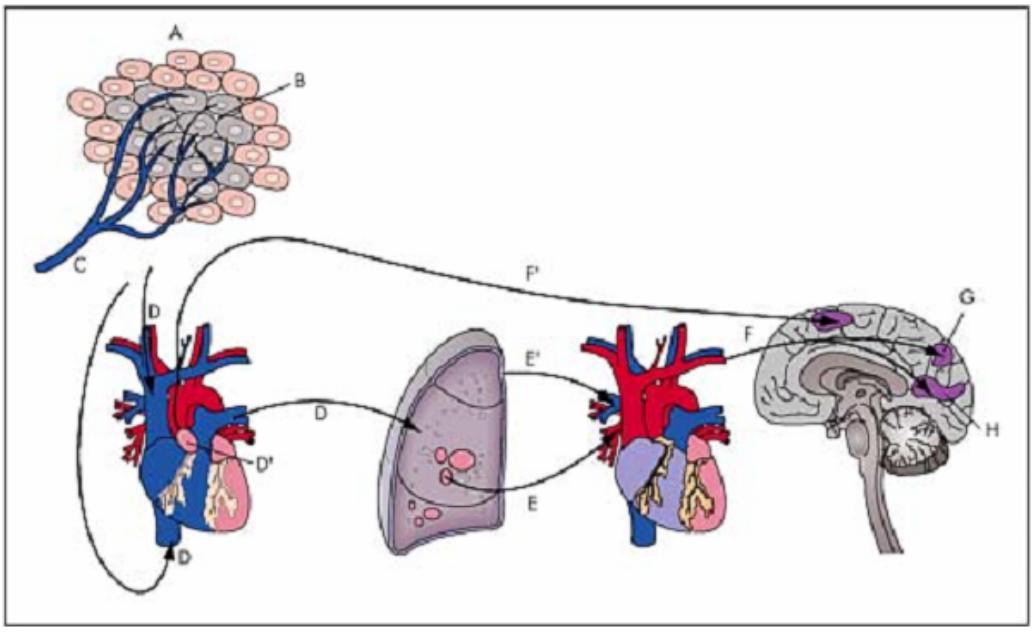

Figure 2

Pathophysiology of the metastatic process. Metastasis is a multistep process. In tins schematic illustration: (A) a malignant neoplasm arises in an organ distant from the CXS -and as it grows, it develops its own vascular supply. (B) Clones of malignant cells with metastatic potential enter blood or lymph channels and eventually reach the venous circulation. (C) The malignant cells enter the right heart with the venous circulation and either exit through the pulmonary artery to the lung (D) or cross a patent foramen ovale to enter the systemic circulation.. Most tumors that enter die lung either arrest in the pulmonary capillary bed, grow as pulmonary metastases - and subsequently seed the pulmonary venous circulation, or (E) alternatively transverse the pulmonary vascular bed without arresting (E') to enter the pulmonary' venous circulation. Malignant clones in the pulmonary venous circulation then enter the left heart and exit into the systemic circulation (F i: along with those cells that may have crossed a patent foramen ovale (F). Once in the systemic circulation, the likelihood of entering, the cerebral circulation is high because, in the resting state. 15-20°b of cardiac output supplies the CNS. (G. H) Tumor cells entering the cerebral circulation must then arrest in brain capillaries or venules. Cross the vessel wall and grow within the brain.[21]

Accordingly many patients with brain metastases either have primary lung tumors or lung metastases at the time of brain lesions become symptomatic. To reach the arterial circulation, the tumor must either: (1) grow in the lung and seed the-pulmonary venous circulation (2) traverse the lung capillary bed to enter the left side of the heart, or (3) cross a patent foramen ovale to enter the left heart directly where tumor cells can then enter the arterial circulation (an extraordinary case report illustrates a tumor embolus that occluded the middle cerebral artery and a second embolus within an open foramen ovale).[22]

Two factors promote intracranial metastases:

(1) In the resting state, the brain receives 15-20% of the body's blood flow, thus making it likely that circulating tumor cells will reach the brain.

(2) Certain tumor cells find the brain a propitious place for arrest and growth,the seed and soil hypothesis posits that tumor cells (the seed) must find an organ (the soil) that supports their growth in order to become a metastasis.This is one of the reasons that the probability of brain metastasis varies among tumor types and that the site of a brain metastasis may vary depending on the histology of the primary tumor. For example, certain primary tumors such as those from the kidney and colon are more likely to metastasize to the cerebellum than are lung cancers or those arising elsewhere in the body (Fig. 3), although other reports disagree with this reported preferential distribution.Once in the intracranial cavity; the tumor must arrest within the capillary bed, cross the capillary bed, grow within the organ, vascularize itself through the process of angiogenesis and then grow large enough to cause symptoms. At each step in the metastatic process, the tumor cells may fail, so that only 0.01% of cells that reaches the circulation ever become metastases.[23]

Tumors may metastasize to virtually any portion of the intracranial cavity (Fig .3).

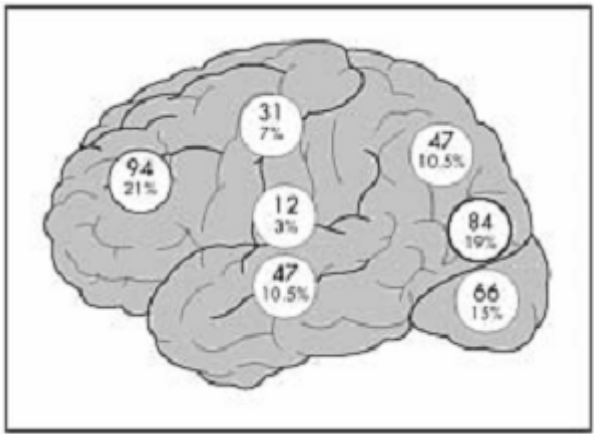

Figure 3

Schematic drawing showing the distribution of single metastases to the brain.[24]

The most common site is the brain parenchyma itself but dura, leptorneninges, pituitary and pineal glands can also develop metastases. Although, as indicated above, certain primary tumors have a predilection to metastasize to certain portions of the nervous system, the overall distribution of brain metastasis is also determined by the size of the region and its vasculature.[25]

Thus, about 85 % of brain metastases are found in the cerebral hemispheres usually in the posterior portion of die hemispheres at the watershed between the middle and posterior cerebral arteries. There is also an over representation in the anterior border zone between the anterior and middle cerebral arteries.[26]

About 10—l5% of metastases are found in the cerebellum. A number somewhat larger man might be expected on the basis of blood supply and probably representing the predilection for some pelvic tumors to metastasize to the cerebellum. Only about 3% of metastases are found in die brainstem.[27]

Several unusual properties of the metastatic process can confuse and confound the physician. For example:

(1) The intracranial tumor may be large but the primary tumor small or undetectable. Several reports describe metastatic brain tumors whose primary was undetectable even at autopsy. The pathogenesis is believed to be secretion by the primary tumor of both angiogenic and anti-angiogenic factors. Antiangiogenic factors in the primary tumor may control its growth whereas angiogenic factors secreted by the tumor may accelerate the growth of metastases.[28]

(2) Metastases may be biologically different from the primary tumor. Although metastatic tumors are usually histologically and biologically similar to the primary this is not always true. Even two metastases to the same organ may differ somewhat in their biologic properties. For example, markers such as estrogen receptors may be present in the primary tumor but not the metastasis.

Genetic differences between a primary tumor and its metastasis often exist. For example, transforming growth factor (T.G.F) inhibits metastatic ovarian cancer more than it does the primary tumor. The explanation is that metastases represent clones of the primary tumor that may differ from the bulk of the primary.

Telomerase, an enzyme present in most primary cancers is also expressed in most brain metastases, but the concentration varies markedly. No correlation exists between telomerase concentration and survival.[28]

(3) In patients whose systemic tumor is otherwise controlled, the brain seems to be a more common site for isolated metastatic disease. This cannot be explained by either blood flow or the nature of the C.N.S microenvironment .The blood-brain barrier probably explains this phenomenon in the first half of the 20th century, when no treatment was available for acute leukemia. C.N.S involvement was rare as patients died from uncontrolled systemic leukemia.[28]

As chemotherapeutic agents became effective in controlling systemic disease, the incidence of C.N.S involvement began to rise to the point where it reached almost 50% in patients with acute lymphoblastic leukemia.The chemotherapeutic agents used to treat leukemia were largely water-soluble and did not cross the blood-brain barrier; the few leukemic cells that reached the C.N.S were protected behind the blood-brain barrier where they could proliferate until they produced neurologic symptoms. Prophylactic treatment of the C.N.S by radiation therapy and or intrathecal drugs has again decreased the incidence of CNS metastases from leukemia to under l0%.[29]

This does not mean that leptomeningeal tumor, once established, cannot be treated by systemic water-soluble agents. Once tumor is established, the blood-CSF barrier is disrupted and the C.N.S becomes accessible to treatment with agents that do not normally cross the blood-brain barrier. Furthermore some systemic agents can penetrate an intact blood-brain barrier when given in high doses. Accordingly, high-dose methotrexate delivered systemically for prophylaxis can, in patients with acute leukemia, prevent the development of C.N.S metastatic disease3[20]

The C.N.S as a sanctuary site for microscopic disease now appears to apply to breast cancer, small cell lung and perhaps other cancers. The C.N.S is becoming an important site of isolated relapse in patients with these tumors when a chemosensitive tumor has relapsed in the C.N.S, it does not necessarily mean that the C.N.S disease is resistant to the chemotherapeutic agents that controlled the systemic tumor.The blood-brain barrier may have prevented those tumor cells from ever seeing a significant concentration of the drug, thus preserving the tumor cells intrinsic chemosensitivity to that agent.[31]

PATHOLOGY

Macroscopic Findings:

Intracranial metastases can be categorized by location as skull, dura, leptomeninges and parenchymal brain metastases. Lesions of the brain and leptomeninges account for 80% of intracranial metastases. The majority of brain metastases (approximately 80%) are located in the cerebral hemispheres. The cerebellum (10-15%) and brainstem (2-3%) are less frequently involved.[32]

Most metastases are round, well-demarcated lesions located at the junction of gray and white matter. Metastatic lesions in the brain displace surrounding brain parenchyma as they grow.[22]

Some metastases have a miliary type of distribution throughout the parenchyma. Leaky tumor vessels result in an extensive zone of edema surrounding the tumor. Cystic degeneration, necrosis and areas of hemorrhage are often seen. [33]

Specific tumors may have a more characteristic gross appearance. The metastatic lesions of melanoma, choriocarcinoma and renal cell carcinoma often develop intratumoral hemorrhages. Edema of the adjacent brain parenchyma is often prominent and sometimes disproportionate to the small size of the lesions.[33]

Meningeal carcinomatosis may occur in patients with lung and breast carcinoma, malignant melanoma, and less commonly, with lymphoma, leukemia and other tumors. Leptomeningeal tumors may appear only as thickening or as a decrease in translucency of the arachnoid membrane. Dural tumors may form dural plaques or nodules.[34]

Histopathological Features:

The histopathological features of metastatic lesions are usually similar to those of the primary tumor from which they originate. Although the majority of metastatic lesions may appear clearly demarcated from adjacent brain on both gross and microscopic examination, microinvasion of tumor cells is invariably present. This aspect is particularly evident in metastases of small cell lung carcinomas (SCLC) and melanomas. Brain metastases elicit a number of reactions from the brain parenchyma. Reactive astrocytosis is often present surrounding the metastatic nodules.[35]

The capillaries of brain metastases resemble those of the primary tumor rather than those of the brain. They have gap rather man tight junctions and fenestrated rather than continuous endothelial cell membranes. These vessels form in tumors only a few millimeters in diameter, disrupting the blood-brain barrier and making even small lesions visible on contrast M.R scans.[36]

Vascular proliferation with variable degrees of endothelial proliferation may be seen within and surrounding the tumor masses. This rich neovasculature appears to play a significant role in development and maintenance of the metastatic lesions, and is a major contributory factor to the vasogenic edema that accompanies brain metastases. Necrosis is frequent and macrophage infiltration may be prominent around areas of necrosis.[37]

For a newly diagnosed brain metastasis of unknown origin, adjunctive morphological techniques such as immunohistochemistry are valuable and can guide the search for a primary site. Immunohistochemistry, in conjunction with the clinical history, can define specific cell lineages in the great majority of cases. In cases in which light microscopy and immunohistochemistry are inconclusive, electron microscopy is a useful adjunctive tool to study subcellular structures that may be diagnostic of cellular lineage. Molecular genetic analysis is the latest resource for the complete evaluation of metastatic tumors of unknown origin.[38]

CLINICAL FINDINGS

Signs and symptoms

The symptoms and signs of brain metastasis do not differ significantly from those of most primary brain tumors. There is a proportionately greater amount of edema surrounding brain metastases, which often causes increased intracranial pressure despite relatively small metastatic lesions. *Signs and symptoms of brain metastases at presentation*.

- Headache. 25%
- Hemiparesis . 20%
- Cognitive and behavioral disturbances. 15%
- Seizures (focal or generalized). 10%
- Ataxia. 10%
- Other. 15%
- No symptoms. 5%

The major difference between the clinical signs of primary and metastatic brain tumors is that metastases usually grow more rapidly than even malignant primary brain tumors, causing subacute symptoms that evolve over a few weeks rather man months. Sometimes, as in primary brain tumors, the symptoms are acute in onset and then either improve or grow progressively worse.[39]

Acute symptoms may be caused by hemorrhage into the metastasis or by a seizure with a prolonged post ictal state.Any intracranial metastatic tumor can bleed, but certain primary tumors, such as melanoma. Thyroid, renal and choriocarcinoma, have a propensity to bleed.[39]