METASTATIC BRAIN TUMORS

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The terms metastatic brain tumor, brain metastasis, or secondary brain tumor refer to cancer that begins elsewhere in the body and spreads to the brain. Brain metastasis can present as a single tumor or multiple tumors. With advances in understanding of the biology of brain metastases, molecularly defined disease subsets and the advent of targeted therapy as well as immunotherapeutic agents offer promise. Future care of these patients will entail tailoring treatment based on host (performance status and age) and tumor (molecular cytogenetic characteristics, number of metastases, and extracranial disease status) factors. The treatment is directed towards not only metastatic brain tumors but their symptoms as well. Longer survival, improved quality of life and stabilization of neurocognitive function for patients with brain metastasis is the goal of treatment. There have been numerous advances in the treatment of metastatic brain tumors in the last decade. These patients often require multidisciplinary care that includes surgical resection, radiation therapy, chemotherapy, and targeted therapies. Complex decisions about the sequencing of therapies to control extra cranial and intracranial disease require input from neurosurgeons, radiation oncologists, and medical/neuro-oncologists. Considerable work involving preclinical models and better clinical trial designs that focus not only on effective control of tumor but also on quality of life and neurocognition needs to be done to improve the outcome of these patients.
INTRODUCTION:
A metastatic brain tumor is usually found when a cancer patient begins to experience neurological symptoms and a brain scan (CT or MRI) is ordered. Less than 10% of all brain metastases are found before the primary cancer is diagnosed. This may happen when a person has an MRI scan for another medical reason, and the brain tumor is “incidentally” found. Occasionally, the person may have neurological symptoms, undergoes a brain scan and has no history of cancer when the brain tumor is detected. Increasingly, cancer patients offered new therapies (i.e., clinical trials) are required to undergo brain imaging, part of what is termed radiologic staging, which may incidentally discover brain metastases. If the site of the primary cancer is not found, this is called an “unknown” primary site. Frequently, the primary site may have been too tiny to be seen or to cause symptoms. In that situation, the metastatic brain tumor is found and subsequently the primary site is discovered. Markers found in the blood, the appearance of the tumor on a scan, and a tissue sample (if surgery is done) help to focus the search for the primary disease site and to guide treatment. With the advances in the genetic profiling of cancers, we are often able to determine the primary cancer resulting in metastatic brain tumor. The metastatic brain tumor usually contains the same type of cancer cells found at the primary site. For example, small-cell lung cancer metastatic to the brain forms small-cell cancer in the brain. Squamous-cell head and neck cancer forms Squamous-cell cancer in the brain. However, recent research is suggesting that some of the tumors develop or acquire new genetic alterations in the primary tumor when they spread to the brain. New biological insights and the development of novel cytotoxic agents and targeted therapies that have better blood-brain barrier (BBB) penetration have elevated the interest in systemic therapies for this clinical challenge. As more effective cancer diagnostics and treatments are developed and as larger numbers of cancer patients longer, an increasing number of cancer patients are diagnosed with metastatic brain tumors. Metastatic brain tumors are the most common brain tumor in adults.

➢ The exact incidence of metastatic brain tumors is not known but is estimated between 200,000 and 300,000 people per year. These numbers are based on data reported by individual hospitals, estimates from a few individual city-based statistics and observations from autopsy results. Research indicates that approximately 10–20% of metastatic brain tumors arise as a single tumor and 80+% as multiple tumors within the brain.

➢ About 85% of metastatic lesions are located in the cerebrum (the top, largest component of the brain) and 15% are located in the cerebellum (the bottom, back part of the brain).

➢ The incidence begins to increase in those ages 45–64 years and is highest in people over 65 years of age.

➢ Although melanoma spreads to the brain more commonly in males than in females, gender does not seem to play a role in the overall incidence of brain metastases.

➢ Central nervous system (CNS) metastasis is not common in children, accounting for only 6% of CNS tumors in children.

CAUSES
Metastatic brain tumors begin when cancer located in another organ of the body spreads to the brain. Cancer cells, visible under a microscope and detectable by a technique called flow cytometry, separate from the primary tumor and enter the circulatory (blood) system. The immune system attempts to destroy these migrating blood-borne cancer cells. However, if the number of cancer cells becomes very high, the immune system may become overwhelmed or tolerant of these cells. Scientists believe circulating tumor cells use the bloodstream or lymph system for access to other organs, initially migrate and enter the lungs, then move on to other organs and in particular, the brain. Some scientists believe cancer cells may break away from the primary cancer site while that cancer is still in its earliest stages. Research shows that these traveling cells (circulating tumor cells) exit the blood or lymphatics and enter another part of the body. In a
new organ, the tumor may lie dormant or rapidly enlarge causing new symptoms referable to the new site of metastasis. The growth of metastatic tumors is often independent of the primary site of cancer from which the tumors originated. In some situations, the process of tumor spread and growth in the metastatic organ occurs rapidly. Since blood from the lungs flows directly to the brain, lung cancer is capable of quickly spreading to the brain. Sometimes, this happens so fast that the brain metastases are found before the primary lung cancer is found. Scientists also know that primary cancers tend to send cells to particular organs. For example, colon cancer tends to metastasize to the liver and the lung. Breast cancer tends to metastasize to bones, the lungs and the brain. It is believed these organ preferences may be caused by small attractant molecules, chemokines that direct and guide tumor cells to the metastatic site. In other instances, cancer cells may be able to adhere, or stick, only to select organs based upon adherent molecules expressed in a particular organ.

**SYMPTOMS**

The symptoms of a metastatic brain tumor are the same as those of a primary brain tumor, and are related to the location of the tumor within the brain. Each part of the brain controls specific body functions. Symptoms appear when areas of the brain can no longer function properly.

Headache and seizures are the two most common symptoms.

The causes of headaches include the metastatic tumor itself that causes distortion of surrounding brain; swelling from fluid leakage through a seizure is a brief episode of abnormal electrical activity in the brain caused by a brain tumor, surgery, or hemorrhage that disrupts brain electrical activity. During normal electrical activity, the nerve cells in the brain communicate with each other through carefully controlled electric signals. During a seizure, abnormal electrical activity occurs, that may stay in a small area or spread to other areas of brain. The result is a partial (or focal) or generalized seizure.

Disturbance in the way one thinks and processes thoughts (cognition) is another common symptom of a metastatic brain tumor. Cognitive challenges might include difficulty with memory (especially short term memory) or personality and behaviour changes. Motor problems, such as weakness on one side of the body or an unbalanced walk, can be related to a tumor located in the part of the brain that controls these functions. Metastatic tumors in the spine may cause back pain, weakness or changes in sensation in an arm or leg, or loss of bladder/bowel control. Both cognitive and motor problems may also be caused by edema, or swelling, around the tumor.

**DIAGNOSIS**

A brain scan may be part of the initial screening process when the primary cancer is diagnosed, or a scan may be ordered if a person living with cancer begins to have symptoms of a brain or spinal cord tumor. Metastatic tumors are diagnosed using a combination of neurological examination and imaging (also called scanning) techniques. A physician may use more than one type of scan to make a diagnosis. MRI or CT is the most commonly available – the use of contrast dye makes the tumor(s) easier to see. Magnetic resonance spectrometry (MRS) is used to measure chemical content in the brain. PET (position emission tomography) scans collect detailed information about the way the tumor uses glucose (sugar), and can help differentiate between healthy tissue, cancer cells, dead disease tissue, and swelling. Full body PET scans can be helpful in identifying the primary cancer site when brain metastases are found first. It will begin to have symptoms of a brain or spinal cord tumor.

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METASTASIS

The images will help your physician learn:
• Size and number of tumors
• Exact location of the tumor(s) within the brain or spine
• Impact on nearby structures

Although scans provide the physician with a “probable” diagnosis, examination of a sample of tumor tissue under a microscope confirms the exact pathologic diagnosis. The tissue sample may be obtained during surgery to remove the tumor, or during a biopsy. A biopsy is a surgical procedure to remove a small amount of tumor for diagnosis.

If a metastatic tumor is diagnosed before the primary cancer site is found, tests to locate the primary site will follow.

MELANOMA METASTASES
• They are the second most common type of brain metastases in men.
• These cancers may metastasize to the brain or the meninges (the covering of the brain and spinal cord).
• Metastases tend to occur several years after the primary melanoma.
• Multiple brain metastases are common.
• Metastatic melanoma tumors are rich with blood vessels that have a high tendency to bleed.

COLON/COLORECTAL METASTASES
• Metastases tend to occur a few years after the primary tumor.
• A single metastatic tumor is common.

KIDNEY/RENAL METASTASES
• Metastases tend to occur within a few years after the primary tumor.
• Single tumors are common.
• The metastatic tumor often contains blood vessels that have a high tendency to bleed.

The three main categories of treatments include surgery, radiation and medical therapy (chemotherapy, targeted therapy or immune-based therapy). More than one type of treatment might be suggested.

When planning treatment, your doctor will take several factors into consideration.
• History of cancer
Status of that cancer
Overall health
Number and size of metastatic tumors
Location of the metastatic tumor(s) within the brain or spine

Early treatment of brain tumor will focus on controlling symptoms, such as swelling of the brain and/or seizures.

- Steroids as Dexamethasone are drugs used to reduce the swelling that can occur around a brain tumor. Reducing the swelling in the brain can reduce the raised brain pressure, and thus temporarily reduce the symptoms of a metastatic brain tumor.
- Antiepileptic (anti-seizure) drugs such as levetiracetam orphenytoin or lacosamide are commonly used to control seizures.

Research shows that the number of metastases is not the sole predictor of how well you might do following treatment. Your neurological function (how you are affected by your brain metastases) and the status of the primary cancer site (i.e. the presence/absence of metastases in other parts of the body) and type of cancer and the genetic alterations in the cancer also appear to influence overall survival. Treatment decisions will take into account not only long-term survival possibilities, but your quality of life during and after treatment, as well as cognition concerns.

**SINGLE OR LIMITED BRAIN METASTASES**
A small number of tumors that are close to each other and if the primary cancer is treatable and under control, treatment plan may include surgery to confirm the diagnosis and remove the tumor, followed by a form of radiation therapy. That radiation may be whole-brain radiation therapy, whole-brain radiation plus stereotactic radiosurgery or stereotactic radiosurgery are applied. This is generally followed by medical therapy (chemotherapy, radiation therapy or immune-based therapy) that may impact not only the primary cancer but also metastatic brain tumor.

**MULTIPLE BRAIN METASTASES**
If patients have multiple brain metastases – four or more brain tumors – and have a known history of cancer, traditionally whole-brain radiation therapy was suggested for these tumors. However, in more recent times there is an increase in the use of radiosurgery or medical therapy (chemotherapy, targeted therapy or immune-based therapy) for these patients. In more recent times there is an increase in the use of radiosurgery or medical therapy (chemotherapy, targeted therapy or immune-based therapy) for these patients. In general, the primary treatment for multiple metastatic brain tumors (or multiple tumors that are not close to each other) is whole-brain radiation. At present, results of chemotherapy are inferior to radiation therapy with or without surgery.
SURGERY
One of the first treatments considered for metastatic brain tumors is tumor removal, or resection. A neurosurgeon – a surgeon specially trained to operate on the brain and spine – will determine if your tumors can be surgically removed by evaluating your health and disease status. Considered to include a single tumor larger than 3 cm.

- Factors supporting (the size of a small pearl), location outside of speech or motor related areas of the brain, and limited and/or somewhat stable disease in other parts of the body. Symptomatic tumors are more likely to be surgically removed.
- Surgery may not be suggested include a tumor that might better respond to radiation, multiple tumors – especially if they are far apart from each other – and tumors in brain locations where specific function resides (so called eloquent brain), for example, language areas. If surgery is not possible or the primary cancer has not been found, a biopsy may still be done to confirm the tumor type. Once the diagnosis is confirmed, radiation and or chemotherapy (depending on the type of cancer) may be part of the treatment plan.

RADIATION
Radiation therapy can be used to treat single or multiple brain metastases. It may be used therapeutically (to treat a metastatic brain tumor), prophylactically (to help prevent brain metastases in people newly diagnosed with small-cell lung cancer or acute lymphoblastic leukemia), or most commonly as palliative (non-curative) treatment (to help relieve symptoms caused by the metastatic brain tumor). Some types of cancer are more responsive to radiation than others. Small-cell lung tumor and germ-cell tumors are highly sensitive to radiation, other types of lung cancer and breast cancers are moderately sensitive, and melanoma and renal-cell carcinoma are less sensitive. Different types of radiation can be used for metastatic brain tumors.

WHOLE-BRAIN RADIATION
Whole-brain radiation is a common form of radiation for metastatic brain tumors, especially when multiple tumors are present, and has been used for several decades. It is delivered in 5-15 doses called “fractions.” By dividing the doses in smaller amounts, the normal brain is somewhat protected from the toxic effects of radiation. Some drugs like memantine have been used as well in clinical trials to help decrease the deterioration of cognition and thinking associated with whole brain radiation. These approaches are still investigational and not routinely used in clinical practice.

RADIOSURGERY
Radiosurgery focuses high doses of radiation beams more closely to the tumor than conventional external beam radiation in an attempt to avoid and protect normal surrounding brain tissue. This approach is most commonly used in situations where the tumor is small and in eloquent regions of the brain, for example, speech and motor localized areas.

BRACHYTHERAPY
Interstitial radiation, or brachytherapy, is the use of radioactive materials surgically implanted into the tumor to provide local radiation. This technique is rarely utilized today for brain metastases.

RADIOENHANCERS
Radio enhancers or so-called radiation sensitizers are compounds which make the tumor more sensitive to the effects of radiation, are under investigation. Sometimes, the addition of chemotherapy prior to, or during, radiation treatment can also have this effect.

CHEMOTHERAPY
It has not often been used to treat metastatic brain tumors due to the blood-brain barrier and drug resistance. Chemotherapy may be combined with other therapies such as radiation. Some tumors that are sensitive to chemotherapy in other parts of the body may become resistant to the chemotherapy once in the brain. The cause for this resistance is unknown. A different drug may be considered if you received chemotherapy for your primary cancer, or a different type of therapy may be considered.

INTEGRATIVE HEALTH CARE
Treatment and supportive areas may include diet, exercise, stress reduction, lifestyle enhancements, massage, acupuncture herbs, mind-body therapies and spiritual growth, among others.
FOLLOW-UP
Follow-up scans are usually then done every two to three months for a year, then as often as your doctor feels is appropriate for you. The scans are used to monitor your tumor’s response to treatment, and to watch for possible tumor recurrence. Metastatic brain tumors, just like tumors elsewhere in the body, may recur. That’s why it is important for cancer survivors to continue their regularly scheduled health visits, even long after their cancer is under control. Treatment for a recurrent metastatic brain tumor begins with updated scans, an evaluation of the person’s overall health and the status of their primary cancer, and their response to previous treatments. Options may include another surgery, another course of radiation therapy, a different form of radiation therapy, a course of chemotherapy, or perhaps a clinical trial.

SUMMARY & CONCLUSIONS
The treatment of patients with brain metastases requires a multidisciplinary team approach in which treatment recommendations (surgery, WBRT, SRS, and systemic therapy) are based on host (performance status and age) and tumor (type and subtype of tumor, number of metastases, and extracranial disease status) factors. An individualized plan to improve the outcome of patients with this life-limiting complication is optimal. Molecularly defined disease subsets and targeted therapies as well as immunotherapeutic agents will aid in improved outcomes in patients with brain metastases. WBRT retains an important place in the management of this disease, but its application and role are being rapidly redefined.

REFERENCES


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