

AMERICAN BRAIN TUMOR ASSOCIATION

Metastatic Brain Tumors



American
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ACKNOWLEDGEMENTS

ABOUT THE AMERICAN BRAIN TUMOR ASSOCIATION

Founded in 1973, the American Brain Tumor Association (ABTA) was the first national nonprofit advocacy organization dedicated solely to brain tumor research. For nearly 45 years, the ABTA has been providing comprehensive resources that support the complex needs of brain tumor patients and caregivers, as well as the critical funding of research in the pursuit of breakthroughs in brain tumor diagnosis, treatment and care.

To learn more about the ABTA, visit www.abta.org.

We gratefully acknowledge Manmeet Ahluwalia, MD, FACP, Director Brain Metastasis Research Program, Burkhardt Brain Tumor NeuroOncology Center, Taussig Cancer Institute, Cleveland Clinic for his review of this edition of this publication.

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Metastatic Brain Tumors

INTRODUCTION

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.

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.

METASTASIS means one tumor.

METASTASES is plural – it means two or more tumors.

METASTASIZE is the process of cells traveling through the body to reach another part of the body.

PRIMARY SITE refers to the location of the original cancer.

Lung, breast, melanoma (skin cancer), colon and kidney cancers commonly spread to the brain.

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. Fewer 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.

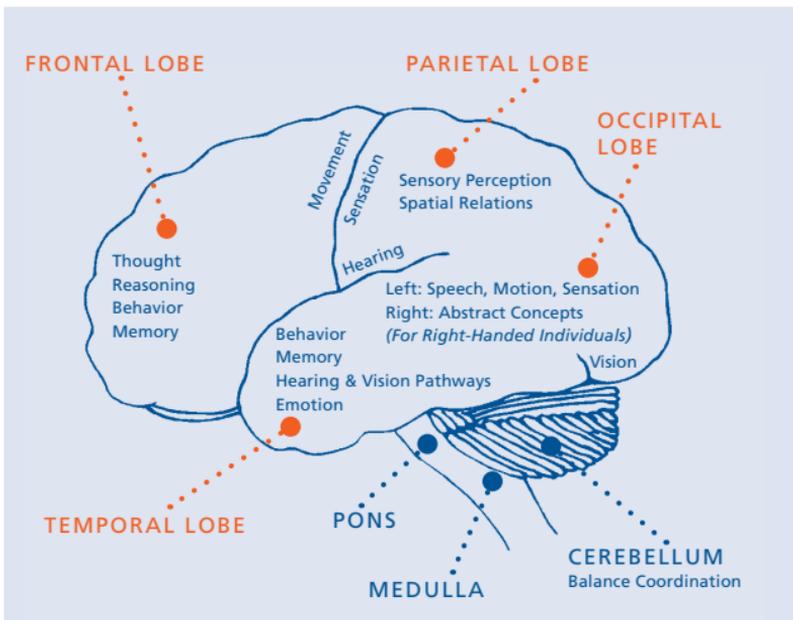
The metastatic brain tumor usually contains the same type of cancer cells found at the primary site. For example, small-cell lung cancer metastatic to the brain forms small-cell cancer in the brain. Squamous-cell head and neck cancer forms squamous-cell cancer in the brain. However, recent research is suggesting that some of the tumors develop or acquire new genetic alterations in the primary tumor when they spread to the brain.

INCIDENCE

As more effective cancer diagnostics and treatments are developed, and as larger numbers of cancer patients

live 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. The American Brain Tumor Association has funded research into the incidence and prevalence of these tumors.
- 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



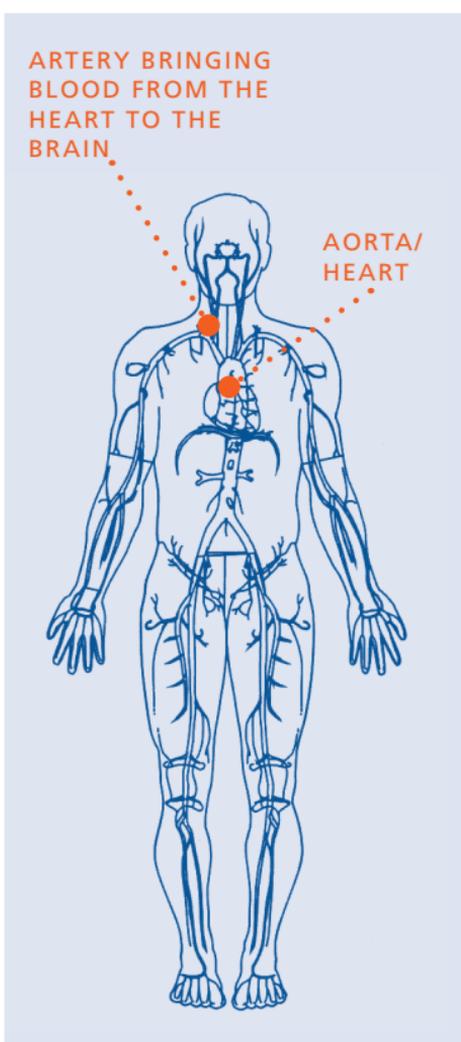
Functions of the lobes of the brain

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.

CAUSE

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



Arterial blood flow

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 (also called edema) from fluid leakage through

tumor blood vessels and compression of the brain due to the growing tumor. Headaches may also be related to bleeding, which can require surgery. While swelling around the tumor is more common, bleeding from ruptured blood vessels in the tumor occurs in a small percentage of patients. Headaches may also be caused by cystic (water filled cavities) changes in the tumor or by interruption of spinal fluid circulation in brain resulting in a condition called hydrocephalus.

- 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 behavior 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.

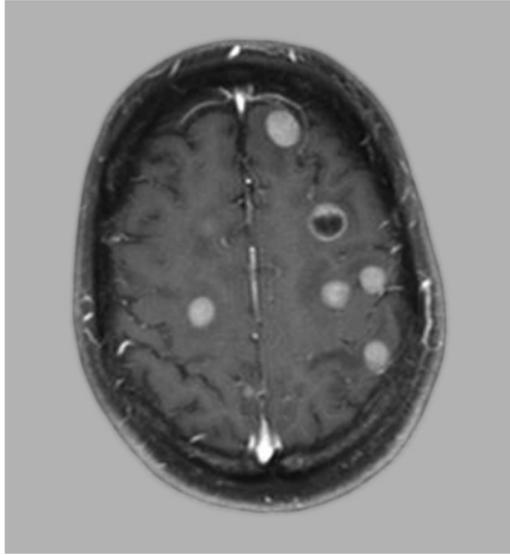
DIAGNOSIS

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



Multiple metastases from melanoma
MRI courtesy of Dr. Chamberlain

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. Your physician will determine the type of imaging most appropriate for you.

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.

SPECIFIC TYPES OF METASTASES

LUNG CANCER

- They are the most common type of brain metastases in both men and women.
- The brain tumor is often found before, or at the same time, or soon after the primary lung tumor (average six to nine months).
- Multiple brain metastases are common.

BREAST CANCER

- They are the second most common type of brain metastases in women.
- Metastases tend to occur a few years after the breast cancer is found (average 2–2½ years), but metastases at five or 10 years post treatment are not unusual.
- They are generally found in younger and premenopausal women.
- They are more common in women with triple negative or HER2/neu positive breast cancer.
- Two or more metastatic brain tumors are common.

TREATMENT

Once your scan shows a suspected brain tumor, your next step will likely be a consultation with a neurosurgeon, radiation oncologist or medical / neuro-oncologist. The neurosurgeon will look at your scans to determine if the tumor(s) can be surgically removed, or if other treatment options would be more reasonable for you.

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 is found.
- 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 your treatment, your doctor will take several factors into consideration.

- Your history of cancer
- The status of that cancer
- Your overall health
- Number and size of metastatic tumors
- Location of the metastatic tumor(s) within the brain or spine

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

- Steroids (most commonly dexamethasone or decadron) 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 or phenytoin 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

If you have a limited number of metastatic brain tumors (generally one to three tumors, or a small number of tumors that are close to each other) and if the primary cancer is treatable and under control, your 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 alone. 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 you 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. If there is a question about the scan results or the diagnosis, a biopsy or surgery to remove the brain tumors may be done. This will allow your physicians to confirm that the brain tumors are related to your cancer. If you do not have a history of cancer, your physicians will order tests to try to determine the primary site. If no other cancer site is found, surgery to obtain a tissue sample may be performed.

In general, the primary treatment for multiple metastatic brain tumors (or multiple tumors that are not close to each other) is whole-brain radiation. The goal of this therapy is to treat the tumors seen on scan plus those that are too small to be visible. As a result, whole-brain radiation may be both preventive and therapeutic.

There is increasing interest in the role of chemotherapy for metastatic brain tumors, though at present, results of chemotherapy are inferior to radiation therapy with or without surgery. A neuro-oncologist or a medical oncologist specializing in the treatment of brain tumors can help determine if this additional therapy would be of help to you.

SPINAL METASTASES

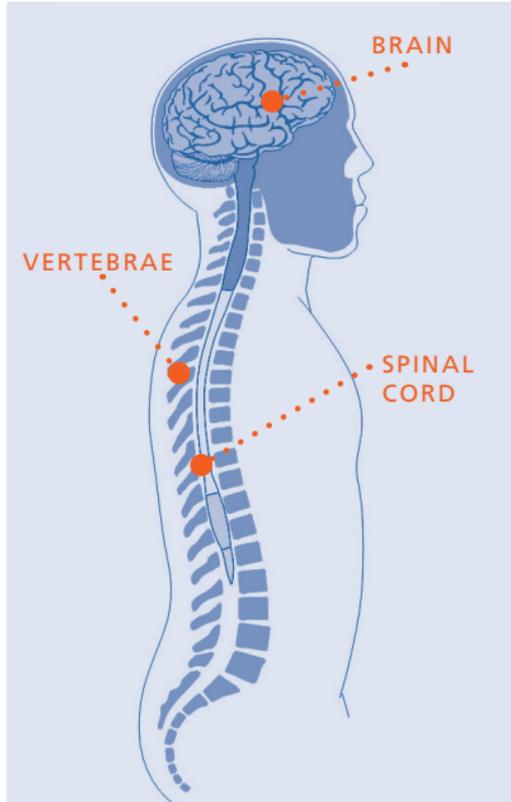
Metastases to the spine are most often caused by lymphoma, breast, lung or prostate cancers. These metastatic tumors usually involve the bones of the spine – the vertebrae – and then spread and encroach upon the spinal cord. Radiation therapy alone, or surgery plus radiation, may be used to treat metastatic tumors to the spine.

MENINGEAL METASTASES

Spread of cancer cells to the meninges, the covering of the brain and spine, and the cerebrospinal fluid (CSF) within which the brain and spine float, is called leptomeningeal metastases (also called carcinomatous meningitis, neoplastic meningitis, leukemic meningitis or lymphomatous meningitis). This type of metastases occurs most commonly with lymphoma, leukemia, melanoma, and breast or lung cancers, and may be treated with radiation therapy or radiation therapy and a regional form of chemotherapy wherein chemotherapy is administered into the water or CSF compartment of the brain (so called intra-CSF chemotherapy). Intra-CSF chemotherapy is administered into the CSF, which is found between the layers of the brain covering, the so called meninges. Intra-CSF chemotherapy may be given by means of a spinal tap or lumbar puncture (intrathecal chemotherapy) or by using a reservoir and catheter (for example an Ommaya device) that is surgically implanted (intraventricular chemotherapy). The

purpose of these devices is to place the chemotherapy drug into the spinal fluid allowing it to “bathe” the cancer cells.

Your doctor will decide which treatment plan is best for you based on your primary cancer, the amount of cancer cells



Brain, spinal cord and vertebrae

present in the spinal fluid, your neurological symptoms and your general medical health.

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.

- Factors supporting surgery include a single tumor larger than 3 cm (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.
- Reasons 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. An important and common concern about whole-brain radiation is its possible impact on cognition and thinking. Research focused in this area is ongoing, and studies indicate that the presence of the brain tumor may cause thinking changes before

treatments even begin. There are novel approaches that spare hippocampus to help preserve memory and decrease the impact of whole brain radiation on cognition and thinking. 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

Recent advances have made stereotactic radiosurgery, also known as LINAC radiosurgery, Gamma Knife or CyberKnife (different machines using a similar method), an effective treatment option for some patients with brain metastases. 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. Small tumors are generally considered to be 3 cm or less in diameter and limited in number. Radiosurgery can also be used to treat tumors that are not accessible with surgery, such as those deep within the brain.

It may also be used for recurrences if whole-brain radiation was previously given, or as a local “boost” following whole-brain radiation.

Radiosurgery given in multiple treatments is called stereotactic radiotherapy.

There are many different pieces of equipment used to deliver radiosurgery; each has a brand name created by their manufacturer. Traditionally radiosurgery was used with surgery in patients with single brain metastasis and in combination with whole brain radiation in patients with 1-4 brain tumors. Recently the role of radiosurgery

is evolving and in select group of patients this modality may be appropriate as single modality in patients with 1-3 brain metastases or in select patients with four or more metastases.

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.

CAN RADIATION BE GIVEN MORE THAN ONE TIME?

Yes, depending on the type, dose and scope of the radiation received the first time. Focused forms of radiation therapy may be used after whole-brain radiation if the tumor is small, or radiosurgery may be repeated if tumor recurs. Your doctor can review your original treatment records and advise if you are a candidate for another course of radiation.

RADIOENHANCERS

Radioenhancers 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

Historically, chemotherapy has not often been used to treat metastatic brain tumors due to the blood-brain barrier and drug resistance. However, new research indicates that it may be an effective treatment modality

for some patients. The decision to use chemotherapy depends on the status of systemic disease, primary site, tumor size and number in the brain, available drugs, and previous history of chemotherapy treatment, if any.

- Recent studies show that some tumors may be sensitive to drug therapy. Small-cell lung cancer, breast cancer, germ-cell tumors and lymphoma are among these tumors. Some new targeted agents for metastatic breast cancer (lapatinib in combination with capecitabine), non-small cell lung cancer (EGFR inhibitors, ALK inhibitors) and melanoma (Mek inhibitors, BRAF inhibitors) may prove useful for brain metastases from these particular cancers.
- There is emerging evidence of immunotherapy (ipilimumab, nivolumab, pembrolizumab) in patients with brain metastases from non-small cell lung cancer and melanoma.
- Intra-CSF chemotherapy (drugs placed within the brain/spine water compartment) may be used for leptomeningeal metastases – cancer cells that metastasize to the covering layers of the brain and spinal cord.

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

Integrative health care brings the physical, mental, emotional and spiritual components of health into the treatment plan, and beyond. Integrative therapies support the health and healing of the whole person. Treatment and supportive areas may include diet, exercise, stress reduction, lifestyle enhancements, massage, acupuncture,

herbs, mind-body therapies and spiritual growth, among others. Many major cancer centers now offer some components of integrative health care. Talk with your healthcare team if you would like to learn more about these complementary approaches.

As in any disease, there are possible side effects from brain tumor treatment. Ask your doctor to explain these effects. He or she can also help you and your family balance the risks against the benefits of treatment.

FOLLOW-UP

After your brain tumor treatment is completed, it will take a few months before the true effects of the treatment can be measured on scan. Most often, the first post-treatment scan is done one to three months after the completion of radiation therapy. This timing allows the full effect of radiation therapy to be evaluated by your physicians.

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.

The chance of a metastatic brain tumor recurring is primarily influenced by the nature and course of the primary cancer, the number of brain metastases, and whether there were metastases to other sites in the body.

If your brain tumor recurs, or if other brain tumors are seen on subsequent scans, a new course of treatment will be planned for you. 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.

FINDING CLINICAL TRIALS

New treatments are developed in organized, carefully overseen testing plans called clinical trials. Clinical trials at times can provide access to novel treatments that may not be available routinely for patients. These trials also can test the new paradigms in treatment for metastatic brain disease. A number of trials are looking at novel treatment options such as targeted therapies or immune based therapies either alone or in combination with radiation and radiosurgery. TrialConnect®, the ABTA's Clinical Trial Matching Service is available at www.abtatrialconnect.org or by calling 877-769-4833.

RESOURCES

Many families living with metastatic brain tumors find assistance through cancer support resources. Support groups allow you to share experiences with others in the same situation. Social workers can help you find these networks, as well as sources of financial assistance, transportation help, home-care needs or hospice programs. Nurses can provide you with information about how to care for yourself or your loved one. Reach out to neighbors, family and friends for help with daily chores. You are not alone – there are extensive resources available to you. If you would like help finding them, please call the ABTA's CareLine at 800-886-ABTA (2282).

THE ABTA IS HERE FOR YOU

You don't have to go through this journey alone. The American Brain Tumor Association is here to help.

Visit us at www.abta.org to find additional brochures, view free, educational webinars on demand, read about research and treatment updates, connect with a support

AMERICAN BRAIN TUMOR ASSOCIATION PUBLICATIONS AND SERVICES

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PUBLICATIONS

About Brain Tumors: A Primer for Patients and Caregivers

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Brain Tumor Dictionary*

Caregiver Handbook*

Returning to Work: Accessing Reasonable Accommodations*

Quick Guide to the Family and Medical Leave Act*

Tumor Types:

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Pituitary Tumors

Treatments:

Chemotherapy

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Conventional Radiation Therapy

Proton Therapy

Stereotactic Radiosurgery*

Steroids

Surgery

Most publications are available for download in Spanish.

*Exceptions are marked **

CLINICAL TRIALS

TrialConnect®: www.abtatrialconnect.org or 877-769-4833

*More brain tumor resources and information
are available at www.abta.org.*

AMERICAN BRAIN TUMOR ASSOCIATION

8550 W. Bryn Mawr Avenue, Suite 550
Chicago, IL 60631

For more information contact:

CareLine: 800-886-ABTA (2282)

Email: abtacares@abta.org

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