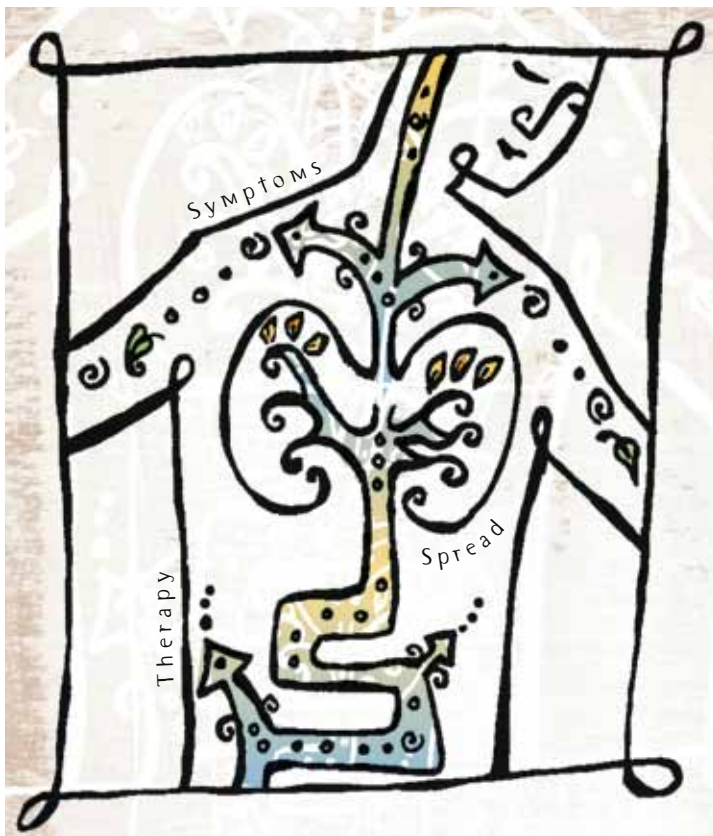


A Patient's **Guide** to **Metastatic Cancer**



What Is Metastasis ■ Identifying Metastases ■ **Managing Symptoms**
■ Treatment Options ■ **Questions to Ask** ■ Resources ■ **and More**

cure

CANCER UPDATES, RESEARCH & EDUCATION

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A Patient's Guide to Metastatic Cancer

WHEN CANCER CELLS BREAK OFF THE PRIMARY TUMOR and travel through the bloodstream or lymphatic system and then grow in a new location, the process is called metastasis. Metastatic cancer, for some but not all tumor types, is considered by many physicians and researchers to be a chronic and incurable disease, but many patients live for a long time and lead functional, fulfilling lives.

TREATMENT AND PROGNOSIS for metastatic cancers are dependent on the location or type of primary tumor, although sometimes the primary tumor cannot be located. When a cancer, such as breast cancer, spreads to another part of the body, such as the lungs, it is still considered breast cancer, not lung cancer.

Most tumor cells don't have the ability to metastasize, and those that do must evolve through several changes in order to establish a new tumor in a different location of the body. First, the cancer cells have to become self-propelled. Cells usually don't move from the place they originate because they cannot move through the body's barrier membranes. However, some tumor cells produce enzymes that eat away at the membranes, softening them enough for the cells to break through.

The direction of blood flow and the size of

the cancer cells cause most to come to rest in the first capillary bed they encounter. Cells that invade the lymph system may be trapped in the first lymph node they enter, which is why the closest lymph nodes are examined to determine if the cancer has spread. The cells may also escape to nearby nodes or grow in distant nodes, a process called skip metastasis.

Many advances in treating metastatic cancer have materialized in the past decade, with drug approvals, clinical trials, prevention, and quality-of-life improvements for people with terminal disease. While many types of metastatic cancer are still considered incurable, certain cancers, such as breast and colorectal, are being transformed into chronic diseases, and patients are living longer with the hopes that those breakthroughs will transfer over to other cancer types.



Predicting Cancer's Spread

IT IS DIFFICULT TO PREDICT WHO WILL DEVELOP METASTASES. The overall stage of cancer, including the size, depth, and whether or not lymph nodes are involved can help estimate the chance that spread may occur. Other indicators, such as tumor grade and new sophisticated genetic and protein tests, can improve the accuracy of risk prediction. All these factors are then used to estimate the risk of recurrence in order to develop a “preventive” plan using adjuvant (after surgery) therapy.

Two commercially available gene-based tests, Oncotype DX and MammaPrint, are used in hormone receptor-positive breast cancer with negative nodes (nodes that show no signs of traveling cancer cells). These types of tests can help estimate the chance of recurrence and provide additional information for deciding if chemotherapy is needed. Adjuvant therapy can include chemotherapy, hormonal therapy, biological therapy, radiation therapy, or a combination depending on the type of cancer. Adjuvant therapy is designed to lower the risk of future metastases, but is not a guarantee against recurrence.

After adjuvant treatment or when surgery alone is used, some cancers require monitoring with specific scans and blood tests, but for other types of cancer, monitoring does not help identify metastases soon enough to have an impact on survival, although therapies may be available that can delay progression of metastases. It's important for patients to discuss details with their medical team about the long-term

treatment and monitoring plan.

Patients should also ask their doctor for a list of symptoms to watch for to identify potential metastasis. Symptoms such as bone pain, persistent cough, and headache can be signs of metastatic cancer, but can also point to a number of less-threatening ailments. The most common site for metastasis is bone, but cancer can also spread to the brain, lung, or liver. Doctors typically control symptoms with supportive care drugs, while support groups, friends, and family can help maintain normalcy to help patients live life to the fullest (see “Symptoms of Metastasis”).

While metastatic cancer is commonly diagnosed after persistent symptoms send a patient to the doctor, sometimes there are no symptoms and the cancer is detected by routine scans, such as X-rays, or blood tests (see “Identifying Metastatic Cancer”).

While some patients find it helpful to know the probability of metastasis, others prefer not to know detailed figures. Either way, no completely accurate method exists to predict if cancer will spread since many complex biological factors come into play that determine long-term outcome.



Identifying Metastatic Cancer

SOMETIMES A PATIENT'S PRIMARY CANCER is only discovered after metastasis causes symptoms. And for those who have already been through treatment for a primary tumor, the fear of recurrence can weigh heavily, especially considering the vague symptoms associated with metastatic disease.

Imaging, such as an integrated technique using positron emission tomography and computed tomography (PET/CT), or magnetic resonance imaging (MRI), may be used to identify metastases. Bone scan, the usual screening test for bone metastasis, is much more sensitive than X-ray and reasonably inexpensive. MRI and CT scans are more sensitive than bone scans, but are more expensive and can sometimes lead to false alarms.

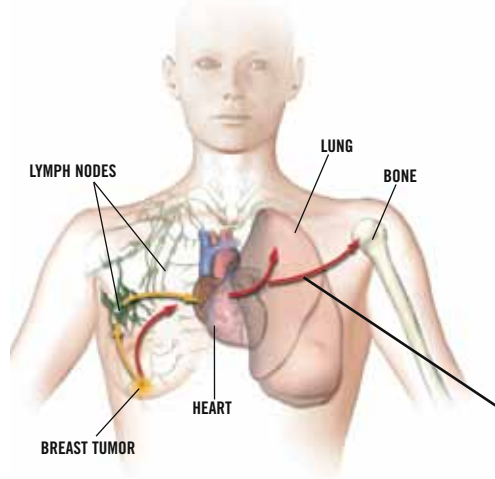
After a suspicious scan, a biopsy is usually done to confirm the diagnosis and a pathologist examines biopsy tissue to confirm a primary or metastatic diagnosis. Pathologists then use specialized diagnostic tests to determine the primary site of the cancer. For survivors, a newly discovered tumor is more often a metastatic tumor than a new primary cancer.

Breast cancer typically moves to the bone (see illustration), liver, brain, and lungs, whereas colorectal cancer usually first spreads to the liver. Lung cancer most often travels to the bone, liver, adrenal glands, and brain, and prostate cancer commonly spreads to the bone and lymph nodes around the pelvic region.

Symptoms depend on where the cancer spreads. An undiagnosed prostate cancer that has spread to the bones in the pelvis

or spine may cause lower back pain before the patient experiences symptoms from the primary tumor. With brain metastases, symptoms can include headaches, seizures, vomiting, and dizziness. Swelling of the abdomen, weakness, weight loss, and jaundice can be signs of liver metastases; and pain, fractures, and breaks can signal bone metastases. Shortness of breath and coughing can be symptoms that cancer is in the lungs.

HOW CANCER SPREADS ►



1
BREAST CANCER CELLS can spread to other parts of the body through the lymphatic system [yellow arrows] or the bloodstream [red arrows].



Symptoms of Metastasis

PATIENTS FACE BOTH PHYSICAL and psychological issues in dealing with metastatic cancer. Some of the more common complications of distant cancer growth include fractures, weight loss, and sleep disorders, as well as others detailed here.

PHYSICAL

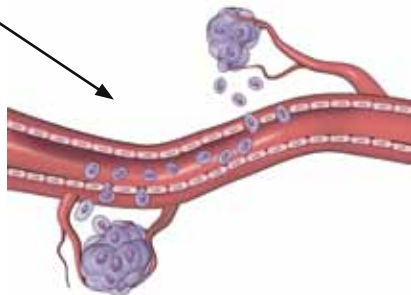
Bone > The most common site for metastasis is bone, causing pain, weakened bones, rare spinal cord compression, and increased risk of fractures and breaks. Around 80 percent of bone metastases grow from cells originating in breast, lung, or prostate tumors, and more than half of all patients with metastases have cancer that has spread to the bone.

Drugs called bisphosphonates can strengthen the bone by inhibiting the ability of cells called osteoclasts from resorbing calcium from bone. Bisphosphonates are used to prevent osteoporosis and are commonly given to patients with multiple myeloma or metastatic breast cancer to increase bone density and help protect against fractures and breaks. Aredia (pamidronate) and Zometa (zoledronic acid) are bisphosphonates that can help prevent skeletal complications caused by bone metastases. Side effects of this class of agents are mild and include flu-like

symptoms. Kidney failure and osteonecrosis (when the bone tissue dies because of lack of blood flow), particularly of the jaw, are rare but serious side effects linked to bisphosphonate use.

While bisphosphonates target bone destruction, Quadramet (samarium) is a radioactive isotope that reduces bone pain by targeting new bone formation. The agent is absorbed in areas of bone tissue where cancer is attacking the bone. Patients receiving Quadramet require less pain medication and may experience relief as soon as one week after the single injection.

When cancer metastasizes to the spine, it can cause spinal cord compression, a severe complication in which the growing cancer squeezes the spinal cord, causing possible numbness or weakness in the legs, numbness in the abdominal area, trouble with the bowel or bladder, or even paralysis. Surgery can reduce the pressure on the spine and decrease the risk of paralysis. Radiation therapy may also be used either following or instead of surgery to halt the side effects of cord compression. A treatment that involves minimal surgery is kyphoplasty, a procedure in which a small balloon is placed within the collapsed vertebrae and slowly inflated. The balloon is then used as a mold for bone cement to preserve the space, and generally takes less than an hour to treat one fracture.



2

*WHEN CANCER SPREADS through the blood, cancer cells detach from the primary tumor and **squeeze through the blood vessel wall** to enter the bloodstream. The cancer cells must again travel from the inside of the blood vessel and into distant body tissues.*

In most patients, regular exercise may be recommended to prevent muscle wasting and maintain bone mineral density, but caution is needed for patients with brittle bones. Calcium and vitamin D supplements can help maintain bone mass at recommended doses of 500 mg of calcium a day and 400 to 800 units of vitamin D, a dose included in most over-the-counter multivitamins.

Brain > Metastases to the brain can cause headache, seizure, vision loss, numbness, or weakness. Some lesions can be removed surgically; otherwise, radiation therapy is used and may result in a full, though usually temporary, remission in the brain.

Tumor cells that spread to the lining of the brain and spinal cord (called meninges) can be treated with radiation or intrathecal chemotherapy delivered straight to the spinal fluid. Steroids are also commonly used to relieve side effects of brain or meningeal metastases.

Liver > Liver metastases can cause abdominal pain, bloating, weight loss, and jaundice (yellowness of the skin or eyes due to liver failure). The best candidates for surgical resection are patients with fewer than four lesions that are less than 5 centimeters in size. Less invasive procedures used include radiofrequency ablation, cryotherapy, and hyperthermia (treating tumors with heat).

Lung > Lung metastases can cause cough, shortness of breath, or chest pain. Fluid can build up if the pleura (the lining of the lung) is involved. Drainage of the fluid with a needle or temporary tube may be necessary.

PSYCHOLOGICAL

Depression > Feelings of sorrow, fear, and anxiety are normal emotions when living with metastatic cancer. But depression, a feeling of overwhelming sadness or anxiety that does not lessen over time, should not be ignored. Clinical depression, characterized by feelings of hopelessness and despair that involves such physical symptoms as loss of appetite and insomnia, can be treated with psychological counseling, help from support groups, and antidepressant medications.

Selective serotonin reuptake inhibitors—Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine)—target neurotransmitters and work to block the reabsorption of serotonin into the nerve cells, making more of the chemical available in the brain. Side effects can include headache, difficulty sleeping, decreased libido, and upset stomach.

Serotonin and norepinephrine reuptake inhibitors, such as Effexor (venlafaxine), inhibit reabsorption of both serotonin and norepinephrine, thus increasing levels of both chemicals in the brain. Side effects of Effexor can include increased blood pressure, nausea, and insomnia. Another type of antidepressant, Wellbutrin XL (bupropion) acts by increasing levels of dopamine, another neurotransmitter in the brain thought to contribute to depression, as well as norepinephrine.

Sleep Disorders > Patients with metastatic cancer may experience insomnia, lack of quality sleep, overwhelming daytime sleepiness, sleep apnea, or waking up throughout the night. Pinpointing the cause of a patient's sleep disorder is necessary



Treatment for Metastatic Cancer

before treating it because symptoms of cancer and treatment side effects, such as coughing or pain, can restrict deep sleep. If the cause is treated, the sleep disorder will correct itself, but poor sleep hygiene will need to be addressed with behavioral therapies.

Complementary therapies, such as acupuncture or imagery, may be helpful. Studies have also shown exercise during the day, relaxation techniques, and yoga can also help patients get to sleep. Newer sleep aids, including Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone), and Rozerem (ramelteon), have little or no risk of becoming addictive and can help patients get needed sleep while working on alleviating symptoms or behavioral therapies to sleep better.

Coping with Symptoms > Keeping a log of symptoms and how they are being treated can help patients and their medical team in making decisions about monitoring and therapy. Patients may sometimes need to try different medications before finding one that works best for them.

Patients deal with metastatic cancer in different ways. Some may feel comfortable keeping their daily routine, while others may want to plan for their final days by looking into hospice care and funeral arrangements, whether the prognosis is weeks or years.

Patients should have a candid discussion with their health care provider to outline their expectations on quality-of-life issues, such as side effects of treatment, survival, whether to participate in a clinical trial, or how to join a support group.

BECAUSE METASTATIC CANCER IS

INCURABLE, doctors focus on stabilizing the tumor and reducing side effects caused by the cancer. Therapies used for metastatic cancer can sometimes cause the tumor to shrink and thereby improve symptoms, but it's difficult to predict who will respond and how long the response might last.

For some types of cancer, remission can be permanent and curative, but for most patients, the cancer will eventually return. The amount by which life may be extended is also difficult to know in advance, and treatment decisions are usually made based on improvement in quality of life and tumor response, incorporating scans, symptoms, and blood work. If the cancer progresses or side effects are too severe, other treatment choices may be recommended. For metastatic cancer with minimal spread to the liver, lung, nodes, or brain, surgery to remove the lesions can be curative in a minority of patients.

Since new therapies are often initially tested in patients with advanced disease, most cancer drugs are first approved for that indication, even if they only provide modest benefit. Researchers believe small advances in treating metastatic disease will continually extend survival and tumor response rate in patients with advanced cancer.

In addition to various standard treatments for metastatic cancer, many of the newer targeted agents have seen at least minimal success, including those discussed here.

CHEMOTHERAPY

Chemotherapy has been one of the mainstay treatments in cancer for decades. Different agents are used depending on the type of cancer, the overall condition of the patient, and prior therapies the patient received.

Newer chemotherapies and combinations, including those with targeted agents, have seen survival benefit in various tumor types. Some of the more recent chemotherapies are oral, reducing the time spent for inpatient infusion treatments. Side effects can include those traditionally associated with chemotherapy, such as hair loss and nausea and vomiting, as well as others.

Depending on the type and stage of cancer, chemotherapy may be given with curative intent or to improve the long-term cure rate after surgery. For noncurative cases of advanced cancer, chemotherapy is given to slow down or shrink cancer in order to improve cancer-related side effects and quality of life.

Many chemotherapy drugs are approved for more than one cancer, including Xeloda (capecitabine), an oral drug approved for both metastatic breast and colorectal cancers. For metastatic breast cancer, Xeloda can be combined with another chemotherapy agent called Ixempra (ixabepilone), which was approved in October 2007. Designed to inhibit a cancer growth pathway, Ixempra is a semisynthetic analog of epothilone B, a new class of chemotherapy. Side effects can include constipation and neuropathy.

Some standard chemotherapy agents for metastatic cancer have improved over the years, including Doxil, a reformulation of Adriamycin (doxorubicin), and Abraxane, a reformulation of Taxol (paclitaxel).

Researchers improved drug delivery of doxorubicin by encasing it in a fat bubble called a liposome, which protects the drug from immune cells until it reaches the tumor. Releasing the majority of the drug near the tumor site also protects healthy tissue. Side effects of Doxil include low blood counts, hand-foot syndrome, and mouth sores.

Taxol is formulated with the potentially toxic solvent Cremophor to make paclitaxel water soluble. Abraxane, on the other hand, uses albumin, a natural protein found in the body, to deliver the drug through the bloodstream. Side effects of Abraxane include low blood counts and neuropathy. Studies suggest Doxil and Abraxane may be more effective than their older counterparts.

An investigational chemotherapy, satraplatin, has shown responses in advanced hormone-refractory prostate cancer. The Food and Drug Administration delayed review of the drug in early 2007 until results of a phase III trial are announced. A third-generation platinum agent, satraplatin's activity involves binding to cancer cells' DNA to prevent cell division, ultimately halting cancer growth. Side effects include diarrhea and myelosuppression. Satraplatin is also being examined in ovarian and lung cancers.

Researchers continue to develop new chemotherapy agents and are testing them in combination with novel biologically targeted agents that are individualized based on sophisticated tests.

HORMONAL THERAPY

Certain hormone-sensitive cancers, including breast, prostate, and uterine, respond well to hormonal therapy, which typically have fewer side effects than chemotherapy. In breast

cancer, the more slow-growing tumors that are positive for estrogen or progesterone receptors are first treated with hormonal therapy, followed by chemotherapy if hormonal therapy isn't effective.

Patients with advanced breast cancer that has progressed on tamoxifen may benefit from aromatase inhibitors Femara (letrozole), Aromasin (exemestane), and Arimidex (anastrozole). When tamoxifen and the aromatase inhibitors fail to work, Faslodex (fulvestrant), a different anti-estrogen agent, may be prescribed.

In prostate cancer, the goal of hormonal therapy is to decrease production of testosterone or block its effect on prostate cancer cells. For patients whose cancer has spread, Lupron (luprolide) or Zoladex (goserelin) are approved hormonal agents that can slow cancer growth or cause tumor shrinkage.

BIOLOGICAL THERAPY

EGFR Inhibitors > Tarceva (erlotinib) is an epidermal growth factor receptor inhibitor approved for metastatic lung and pancreatic cancers, both hard-to-treat and usually diagnosed after the cancer has spread to other parts of the body. Studies have shown the drug can extend survival in both cancers.

Another EGFR inhibitor, Erbitux (cetuximab), is an antibody that can be effective in slowing down metastatic colorectal cancer, namely because EGFR is found in abundance in about 80 percent of colorectal cancers. In studies of Erbitux and Camptosar (irinotecan), the combination reduced tumor size in 23 percent of patients and extended progression-free survival to four months. After the FDA reviewed phase III data showing that Erbitux

improved overall survival, the agency approved the drug in October 2007. Erbitux is the first approved single-agent biological therapy to improve overall survival in metastatic colorectal cancer. Side effects can include low blood pressure, rash, and weakness. Erbitux has a second indication for advanced head and neck cancers, and is currently being tested in sarcoma, esophageal, gastric, and breast cancers.

While Vectibix (panitumumab), an EGFR inhibitor that also targets metastatic colorectal cancer, did not show an improvement in overall survival in patients with resistant metastatic colorectal cancer, the drug did shrink tumor size in 8 percent of patients and extended the time to disease progression or death from 60 days with standard care to 96 days. A major side effect with Vectibix, as with other EGFR inhibitors, is rash, in addition to nausea, diarrhea, and fatigue.

Antiangiogenics > Some tumors secrete a protein called vascular endothelial growth factor that signals blood vessels to grow toward the tumor to provide oxygen and nutrients. Antiangiogenic drugs block this process, and, in combination with traditional chemotherapy, can delay growth and shrink tumors.

The first approved antiangiogenic drug was Avastin (bevacizumab) for metastatic non-small cell lung and colorectal cancers. The latest results of the AVOREN trial, announced at the 2007 annual meeting of the American Society of Clinical Oncology, found patients with metastatic kidney cancer treated with interferon and Avastin had a 59 percent improvement in progression-free survival compared with patients receiving



Planning for End of Life

only interferon. Avastin also can delay time to progression when added to chemotherapy for breast cancer and is currently being evaluated for FDA approval for advanced breast cancer. Side effects of Avastin include high blood pressure and rare incidences of hemorrhage, stomach perforation, and blood clots.

HER2 Inhibitors > Breast cancer drugs Herceptin (trastuzumab) and recently Tykerb (lapatinib) were initially approved to treat HER2-positive metastatic cancer because of their ability to delay disease progression. Herceptin received a second approval in 2006 for early-stage breast cancer to prevent recurrence, and researchers think it's likely the same will happen with Tykerb.

Herceptin and Tykerb both target HER2, a protein overexpressed in some breast cancers, but Tykerb blocks HER2 and HER1 (also known as EGFR), both of which promote cell growth.

Researchers are beginning to see benefit with Tykerb in patients whose breast cancer has spread to the brain. Because Tykerb is a small molecule, as opposed to the large monoclonal antibody Herceptin, researchers believe it stands a greater chance of squeezing through the blood-brain barrier into the brain where most drugs are too large to enter. A phase III study of Tykerb in women with brain metastases found nearly half had at least a 20 percent reduction in brain lesions. Side effects of Herceptin include fever, nausea, and rarely, heart damage; side effects of Tykerb include nausea and vomiting, diarrhea, and fatigue.

IDEAL END-OF-LIFE CARE ALLOWS A PATIENT DIGNITY, without pain and surrounded by friends and family. It means resolving financial issues and includes clear communication between doctor and patient about medical issues and symptom management.

Palliative care focuses on comfort and lessening of symptoms rather than a cure, while integrating psychological and spiritual aspects of care and offering support that will allow a patient to live as actively as possible until death.

Patients are encouraged to research hospice early because one does not need to be near death to enter. Hospice is covered by most insurance plans and Medicare. While a doctor must certify a patient has six months or less to live to get coverage, Medicare does not restrict care after six months. If the prognosis changes, however, hospice can be discontinued and treatment reconsidered.

Some hospices can provide treatment, such as chemotherapy and radiation, as long as it is primarily palliative and supports the patient's quality of life. While most are home-based, with members of the medical care team visiting regularly, some hospices also have inpatient hospital units.

Wills, advance directives, and a health care proxy will give medical personnel and family clear instructions on how the patient wants to handle specific issues when he or she is no longer capable of making decisions. Whether a patient would want a feeding tube, a respirator, or CPR are all questions that should be considered prior to the time when the decision demands immediate attention.



Resources

American Cancer Society

800-227-2345

www.cancer.org

American Pain Foundation

888-615-7246

www.painfoundation.org

BCMets

www.bcmets.org

Cancer Care

800-813-4673

www.cancercares.org

Cancer Supportive Care Programs

www.cancersupportivecare.com/metastatic

Hospice Education Institute/Hospicelink

800-331-1620

www.hospiceworld.org

Hospice Foundation of America

800-854-3402

www.hospicefoundation.org

MetaCancer Foundation

www.metacancer.org

Metastatic Breast Cancer Network

888-500-0370

www.mbcnetwork.org

National Cancer Institute

800-422-6237

www.cancer.gov

National Hospice and Palliative Care Organization

800-658-8898

www.nhpco.org

QUESTIONS TO ASK

- Where did my cancer start and where has it spread?
- What symptoms of metastatic cancer should I be monitored for?
- Can metastatic cancer be prevented?
- What treatment choices are available to manage my disease?
- Which treatment do you recommend, and why?
- Is this treatment intended to help me live longer or to relieve/prevent symptoms of metastatic cancer?
- What side effects may result from the treatment(s) you recommend, and what can be done to help manage these side effects?
- What plans and available therapies should be considered if the cancer progresses on the current treatment?
- Do I qualify for a clinical trial?
- What would happen if I decided to not receive further cancer treatment?

CONTENT BY ELIZABETH WHITTINGTON

COVER ILLUSTRATION BY JAN PULTS