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Beyond the Breast

Two women living with metastatic breast cancer that has spread to the brain describe the tools that are helping to keep them alive.

By MEERI KIM, PH.D.

Flori Hendron was taking a shower when she felt a tiny lump near her armpit. She was 38 with no family history of breast cancer, so she figured the growth would be benign. To be safe, she scheduled a doctor's appointment.

"I followed up on it, and that launched my adventure with breast cancer back in 1996," says Hendron, now 62, a resident of Los Angeles. The mother of two endured a lymph node dissection, a lumpectomy, radiation and chemotherapy to treat her early-stage disease. "I went into that year of treatment like a warrior, even though it beat me up so badly. My kids were 6 and 8, so there was no way I was going to die."

Afterward, she assumed she had won her hard-fought battle with cancer. Instead, it turned out that first small lump marked the beginning of an agonizing, decades-long war. In 2002, a large spongy lump appeared in the same breast, leading to a double mastectomy with reconstruction. In hindsight, Hendron wishes she had skipped the reconstruction. The surgery left her extremely sick with multiple infections, and at the same time, the cancer continued to spread. »

« **FLORI HENDRON**, a survivor of brain metastases from breast cancer, started painting while recovering from her bilateral mastectomy in 2002 and never stopped.

Later that year, after a horrible bout with several chemotherapies that didn't work and spread of the cancer through lymphatic vessels in the skin, Hendron finally started taking Herceptin (trastuzumab), a targeted therapy for patients with HER2-positive breast cancer. She'd known from the start that her cancer was HER2-positive, she says, but was considered ineligible for the drug until 2002 because her tumor was too small and her disease wasn't advanced enough. The drug kept her cancer-free, and after 20 months of treatment, she stopped taking it in April 2004.

"I used to race forward and get things done quickly in my career, and in breast cancer, I did the same thing but with blindfolds," says Hendron, who spent most of her professional life in product design, brand development and marketing. "I should have never stopped the Herceptin, but I just didn't know enough yet."

In 2007, she received a stage 4 breast cancer diagnosis. The disease had spread to her lungs and sternum, and although Hendron also asked for brain imaging to check for metastases, her oncologist at the time dismissed her request as it was not the standard of care in the absence of symptoms. After she switched to a new oncologist, an MRI scan revealed a single brain metastasis in her frontal lobe.

"Over the years, I've learned that if a doctor belittles you or is unsupportive, it's time for a new doctor," she says. "Be a fully active participant in your own survival and insist on what you need."

Nunny Reece, who also is living with stage 4 breast cancer, agrees that patients must advocate for themselves and pay attention to their bodies. She first found a lump in her breast in 2015 at age 37, but her doctor told her that she simply had dense breasts and shouldn't worry.

Two years later, in June 2017, Reece discovered a new lump under her arm. She also noticed blotches on her skin and experienced pain throughout her body. Even though her doctor gave her a diagnosis of lupus, she decided to schedule a mammogram because the pain wasn't going away.

"First they told me I needed to see a surgeon because I have breast cancer. At that time, I had no information other than that it was breast cancer, so I assumed it was early stage," says Reece, now 42, a resident of Hope Mills, North Carolina. "I was so shocked when the doctor told me, with tears in her eyes, that they (couldn't) do surgery because I (was) already at stage 4."

Having lost her father to stage 4 colon cancer just a year earlier, the mother of three felt devastation and heartbreak. The disease — which was hormone receptor (HR)-positive but HER2-negative — had spread to her lungs, lymph nodes and bones. Her doctors first tried hormone therapy, a treatment for breast cancers that are fueled by hormones, but it didn't work. They moved on to oral, then IV chemotherapy drugs, which helped for a while.

In December 2019, Reece experienced frequent headaches and dizziness, common symptoms of brain metastases. An MRI confirmed that the cancer had spread to her brain.

"Brain metastasis is quite common in the metastatic breast cancer setting (in which cancer has spread beyond the breast and nearby lymph nodes), and it is becoming more problematic as we're getting more novel drugs to the market that are doing a better job of controlling systemic disease," meaning cancer throughout the body, says



“You just have to learn to be present. All we have is this moment, and each person has to find what works for them to be in the moment.”

— FLORI HENDRON



“ I trust that one day we’ll have a miracle and be able to beat this thing. I’ll have a good quality of life again and do things with my family like I used to.”

— NUNNY REECE, patient with brain metastases

Dr. Rashmi K. Murthy, assistant professor of breast medical oncology at The University of Texas MD Anderson Cancer Center in Houston. “For patients with HER2-positive, metastatic breast cancer, for example, up to 50% of individuals can develop brain metastases during the course of their disease.”

SPOTTING SYMPTOMS OF SPREAD

More women like Hendron and Reece are living longer with metastatic breast cancer and will at some point require treatment for brain metastasis. Current options, such as radiation and surgery, aren’t a possibility for all patients, depending on the number of tumors, and can have lingering side effects. For many patients, the development of brain metastases greatly limits life quality and expectancy.

Fortunately, new targeted therapies and immunotherapies show promise for brain metastases. These innovations have the potential to treat secondary tumors while minimizing harm to healthy brain tissue and reducing the possibility of negative long-term side effects.

“We’re all taught in medical school that the brain doesn’t regenerate, so it’s very difficult once you have a neurologic symptom to have full recovery, unless it’s very short-lived,” says Dr. Carey K. Anders, medical director of the Brain and Spine Metastases Program at the Duke Cancer Center in Durham, North Carolina. “We don’t want our patients to have to live with a neurologic

symptom that could alter their daily life, whether it affects driving, caring for themselves and their family, (or) doing their work or the hobby that they love.”

Despite all the new therapies that have emerged, breast cancer remains the second most common cause of death in women. Most of those deaths are caused by metastatic breast cancer. Although just 6% of patients have metastatic breast cancer at initial diagnosis, nearly 30% with early-stage breast cancer will eventually develop metastatic disease.

The brain, bones, lungs and liver are common sites of breast cancer metastases. Breast cancer is the second leading source of brain metastases after lung cancer, and 10% to 15% of all patients with the disease will develop at least one secondary brain tumor.

Among patients with metastatic breast cancer, the risk of spread to the brain can be higher depending on the disease’s subtype. Those with HER2-positive disease are the most susceptible, with about half of all patients developing brain metastases. About 25% to 45% of women with triple-negative metastatic breast cancer will develop brain metastases, which also represents an elevated risk of brain metastases compared with non-triple-negative breast cancer. Breast cancers with estrogen receptors, called ER-positive cancers, that are also HER2-negative tend to have a lower risk.

Brain metastases are associated with a poor prognosis. After diagnosis, overall survival ranges from three months »

REECE considers her husband, SCOTT REECE, and three sons her inspiration for trying treatment after treatment to fight breast cancer that has spread to her brain.



to just over two years. Metastases are most often discovered using MRI with a contrast solution delivered intravenously to improve image clarity. Physicians watch for common symptoms of brain metastases in patients when deciding whether to order a scan.

“Symptoms that we look out for are headaches, especially if they happen with nausea and vomiting that can’t be really well explained by a patient’s chemotherapy, for example,” says Dr. Nancy Lin, director of the Metastatic Breast Cancer Program at Dana-Farber Cancer Institute in Boston. “We also worry about seizures, or if someone has weakness on one side of their body.”

RANGE OF THERAPY SIDE EFFECTS

Treatment may involve local therapies directed at the brain metastases, such as surgery and radiation therapy, as well as systemic therapies that treat cancer throughout the body. Surgery could be a viable option for a single, large brain tumor, depending on its location. But for most patients, initial treatment involves either focused radiation

or whole brain radiation, depending on the number of metastases and how early diagnosis occurs.

Because she had a single tumor, Hendron had a noninvasive procedure in February 2008 called Gamma Knife stereotactic radiosurgery, which uses 3D imaging to deliver a powerful, precise dose of radiation to a targeted area. It took just a single outpatient session without any incisions or anesthesia to successfully treat her lesion. Side effects of stereotactic radiosurgery can include fatigue, swelling, headache, nausea and vomiting and usually last for a few weeks after treatment.

“Gamma Knife was the easiest treatment I ever had and the most effective,” Hendron says. “I was in the hospital at 7 a.m. and home by 11 a.m. I wore my own clothes and didn’t need any pre-meds or post-meds.”

Reece had a very different and much more harrowing experience. She had 12 metastases throughout her brain and was treated with 10 rounds of whole brain radiation. Because it delivers radiation to the entire brain, including healthy tissue, this type of treatment can lead to serious problems later in life, such as memory loss, strokelike symptoms and poor brain function. Patients also suffer from painful short-term side effects such as headache, nausea, vomiting, fatigue and hair loss.

“Treatment has not been good to me. It has been a struggle; really, really tough,” Reece says. “The side effects from the whole brain radiation were bad. I was nauseous, throwing up, dizzy. The MRI showed that it did help, though, and some of the metastases in my brain decreased in size.”

Fortunately, advances in local therapies aim to help more patients like Reece reap the benefits of radiation therapy without the harsh side effects. For example, a modification to whole brain radiation that avoids damage to the hippocampus, a region of the brain associated with memory, is now the standard of care at many institutions. Study findings have also shown that Namenda (memantine), a drug originally used to treat Alzheimer’s disease, can help protect the brain and may improve cognitive outcomes in patients undergoing whole brain radiotherapy.

In addition, the number of metastases that can be treated with stereotactic radiosurgery instead of whole brain radiation continues to increase as the technology improves. “When the original radiosurgery studies came out, the number of lesions was three to four that could be treated safely with radiosurgery at one time, and anything more than that required whole brain. We’re now up into the teens,” Anders says. “There is data to support irradiating 10-plus lesions, and I know we’ve been doing

that routinely at our cancer institute to try to avoid whole brain radiation therapy.”

Perhaps the most exciting advance lies in the results of the phase 3 HER2CLIMB clinical trial of Tukysa (tucatinib), a new HER2 kinase inhibitor used to treat HER2-positive breast cancer, in patients with brain metastases. Tukysa crosses the blood-brain barrier, a membrane that separates circulating blood from the brain, which most cancer therapies can't do. Patients who received Tukysa along with chemotherapy and Herceptin experienced a higher rate of tumor shrinkage, including metastases in the brain, and also had a longer period of time where they lived without worsening disease, and lived longer overall, compared with patients who received only standard chemotherapy and Herceptin.

In April 2020, the Food and Drug Administration (FDA) approved Tukysa in combination with Herceptin and Xeloda (capecitabine) based on these findings for previously treated patients with advanced inoperable or metastatic HER2-positive breast cancer.

Several clinical trials focusing on new treatments or combinations for brain metastases are recruiting or plan to recruit patients with breast cancer. For instance, an upcoming phase 2 study will involve genetic testing of the brain lesion to check for alterations that could be matched to a therapeutic target. A phase 3 trial in the recruiting stage will see if combining Tukysa with Kadcyca (T-DM1; ado-trastuzumab emtansine), a targeted therapy for HER2-positive breast cancer, improves survival.

As similar treatments gain FDA approval, improved guidelines around screening will likely emerge to catch and treat brain metastases earlier. Right now, the standard is to screen only patients who have symptoms.

“We are definitely evaluating patients who have any kind of neurological symptoms for brain metastases, but it's not necessarily an immediate part of their diagnostic work-up,” Murthy says. “As we get more and more therapeutics that show efficacy across the blood-brain barrier, I certainly think that is going to change. The approval of tucatinib has certainly changed my practice to evaluate patients for brain metastases.”

SCREENING: PROS AND CONS

The topic of screening for brain lesions has become controversial in the field of breast cancer, mostly because of

a lack of evidence. However, multiple studies in the works will attempt to disentangle the effects of regular brain MRIs on patients with breast cancer.

“We don't have definitive data to say that screening is useful, and screening has the potential to be harmful if it's done in a way that leads to treatment changes that may or may not be necessary,” says Lin, who does not routinely screen patients but has a very low threshold for ordering a brain scan. “People could end up getting (potentially harmful) treatments that they don't necessarily need or getting switched off the treatments that would otherwise have worked. That's the argument against universal screening for brain metastases.”

Hendron and Reece get regular brain MRIs to check for the appearance of new secondary tumors. In 2019, Hendron's doctors uncovered three more brain metastases,

which were treated with stereotactic brain radiation therapy. Since then, her scans have been stable.

“I often say cancer is a mind game. The body game is what the doctors and medicine do, but the mind game is the work we have to do,” she says. “The biggest piece of advice is: You just have to learn to be present. All we have is this moment, and each person has to find what works for them to be in the moment.”

For her, the best self-care activities are art and writing. Hendron started painting while recovering from her

bilateral mastectomy in 2002 and never stopped. She even developed and facilitated an art program at Cedars-Sinai Medical Center, where she taught other cancer survivors how to connect with the healing process through art expression.

Reece, whose cancer remains active in her liver and lungs, started her eighth line of treatment with Halaven (eribulin), a type of chemotherapy used to treat metastatic breast cancer, in September. If that doesn't work, she plans to consider any clinical trials that she might be eligible for. The driving force behind trying treatment after treatment, despite the excruciating side effects and risk of disappointment, is her family: her husband of 20 years and three sons.

“Day-to-day life is a struggle. Some days I'm OK, but my OK is different from everyone else's OK. I'm able to get out of bed today, wash my face, brush my teeth,” says Reece. “But through my relationship with God, I trust that one day we'll have a miracle and be able to beat this thing. I'll have a good quality of life again and do things with my family like I used to.” ■

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