When to *Skip* Surgery

Can mastectomy or lumpectomy be avoided in women with ductal carcinoma in situ?

By DEBORAH ABRAMS KAPLAN

Donna Pinto began getting mammograms at age 40 because her grandmother died of breast cancer at 50. In 2010, a suspicious mammogram led Pinto, then 44, to a needle biopsy in her right breast. The pathology showed ductal carcinoma in situ (DCIS), considered the earliest form of breast cancer. DCIS refers to abnormal cells found only inside a milk duct.

Pinto's surgeon wasn't quite convinced, thinking the results might indicate atypical ductal hyperplasia, a marker for women who might have a risk factor for developing breast cancer. A subsequent surgical biopsy showed intermediate-grade DCIS. Pinto was given two treatment options: full mastectomy or partial mastectomy with seven weeks of daily radiation.

She held off on treatment as she dove into research that revealed varying medical opinions, some saying to avoid treatment unless the diagnosis was high-risk DCIS, and that low- and intermediate-grade DCIS were potentially overtreated and more studies were needed. "That was different from the information I received," says Pinto, who chose active surveillance.

With a rise in breast cancer screening has come a rise in DCIS diagnoses, which make up 20% to 25% of all breast cancers in the United States. More than 60,000 women each year receive a diagnosis of the condition. Labeled a stage 0 cancer, DCIS is considered pre-invasive. »

For ductal carcinoma in situ, **DONNA PINTO** rejected lumpectomy and mastectomy and opted for active surveillance.

How to treat DCIS continues to be debated and researched by the medical community. That's because preventing an invasive breast cancer diagnosis in women with DCIS does not appear to reduce the chances of dying from breast cancer, which has led to concerns about overtreatment. In 20% to 30% of patients who don't receive treatment, DCIS will progress to invasive breast cancer, according to Dr. Mridula George, a medical oncologist treating breast cancer at Rutgers Cancer Institute of New Jersey.

A month after the surgical biopsy, Pinto had a breast MRI followed by two mammograms over the next 18 months. The second mammogram showed potentially invasive cancer, so Pinto underwent two lumpectomies, the second to clean up the margins, which potentially had cancer cells. The diagnosis was low- or intermediate-grade DCIS; a second pathology opinion downgraded it to low-grade. Because the margins were still potentially positive, her doctor again encouraged her to get a mastectomy or at least undergo three weeks of radiation. "I felt like I was being bullied," she says. "I found a new doctor."

The Oncotype DX Breast DCIS Score test, which was new at the time, showed that Pinto was at low risk of developing invasive cancer. Her DCIS has not progressed in 11 years. She started the website DCIS411.com to support and educate other women with the diagnosis.

DECIDING ON DCIS TREATMENT

The discussion about de-escalating surgery for low-grade DCIS and early stage invasive breast cancer is not new, but there's a continuing research focus to determine when it's safe for women to avoid surgery.

Doctors tend to recommend lumpectomy for localized DCIS as a first treatment approach. After surgery, the patient often receives breast radiation. Mastectomy is not typically recommended, says Dr. Alastair Thompson, chief of breast surgery and a researcher at Baylor College of Medicine in Houston. The patient may also be given anti-hormonal therapy or an endocrine medication for longer-term protection against progression and future breast changes.

National Comprehensive Cancer Network (NCCN) guidelines call for performing a lumpectomy at a minimum for DCIS at any stage. "One thing to understand about medicine is that changing practice has to be based on evidence that shows it is not going to be detrimental

DONNA PINTO BY EDER ESCAMILLA

to the patient in terms of future risk of invasive cancer," George says. Currently, physicians cannot accurately predict which patients are at increased risk of progression to invasive cancer.

Women who decline breast surgery can consider taking anti-estrogen (hormonal) therapy to decrease the risk of progression if the cancerous cells express the estrogen or progesterone receptor. So far, preliminary studies support this approach for lower-grade DCIS, but larger studies are needed. "Most patients are more receptive to having the surgery versus taking a pill (long term)," George says. Hormonal therapy has potential side effects. For instance, tamoxifen, the treatment of choice for premenopausal women, can cause fatigue, hot flashes, and a small risk of developing blood clots or uterine cancer.

Women who receive a DCIS diagnosis in their 30s and 40s or have a family history of breast cancer may want to get genetic testing, George says. Those with mutations such as BRCA1 or BRCA2 have an increased risk of DCIS turning into invasive breast cancer, and a bilateral mastectomy might be recommended. A patient who takes that route would not need radiation or hormonal therapy if the tumor is estrogen- or progesterone-receptor positive, George says.

COMPARING STRATEGIES IN CLINICAL TRIALS

"It's ironic that, in the 1990s, the data was saying we can do breast conservation, and surgeons who didn't grow up with that were uncomfortable with it. Women wanted to conserve their breasts," says Dr. Benjamin Anderson, a breast surgeon at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. "Now, the pendulum has swung. More women want bilateral mastectomies, and surgeons are saying you don't need to do that."

Researchers in clinical trials are investigating whether surgery offers a benefit. For instance, the COMET trial, which began in 2016, is comparing surgery with or without radiation, as well as with or without endocrine therapy, to active surveillance with or without endocrine therapy for five years. Researchers want to determine which groups of women with low-risk DCIS might be spared from surgery. Thompson, one of the trial's co-principal investigators, says they've recruited 568 of the 1,200 participants needed. "It will be awhile before we determine what the answer is," Thompson says. After recruiting ends, it will take at least two years of follow-up to reach the first reporting point to determine results.

Two European trials tried to answer the same question but closed early because not enough patients were recruited. "Most folks know they want one treatment or the other and are not willing to be randomized," Thompson says. A Japanese trial is offering active monitoring and tamoxifen, not surgery.

Thompson is also involved with the Precision collaboration, which builds on multiple studies conducted over the past 20 years in the United States, the United Kingdom and Europe. It aims to distinguish features of those with DCIS who will progress versus those who won't.

HANDLING INVASIVE BREAST CANCER

The most common form of breast cancer, invasive ductal carcinoma, makes up 80% of all breast cancer diagnoses. It occurs when cancer that began in a milk duct moves into the breast tissue.

There's flexibility in managing DCIS because the mortality rate is relatively low, according to Anderson. "(But) with invasive breast cancer, now you're talking about a different arena," he says.

Treatments include breast surgery, chemotherapy, radiation therapy, targeted therapy and/or hormonal therapy, depending on the cancer subtype. "These treatment options are used to reduce the chance of the cancer coming back and trying to prevent stage 4 cancer, which is not curable," George says. Not all women need all three approaches.

Women with invasive breast cancer typically get neoadjuvant therapy, which is drug treatment before surgery, to shrink the tumor. Multidrug treatments are so effective in 30% to 50% of some subtypes, particularly for breast cancer that is human epidermal growth factor receptor 2 (HER2) positive or triple-negative, that the cancer »

» **PINTO,** seen here in 2010 with her husband, **GLENN,** older son, **SKYLER,** and younger son, **CODY,** says her DCIS has not progressed in 11 years.

« With her oncologist, **VALERIE FRASER** founded the Inflammatory Breast Cancer International Consortium (ibcic.org) to bring researchers together throughout the world to advance science, medicine and treatment options.

VALERIE FRASER BY LINDSAY JAYE PHOTOGRAPHY

will disappear, so there's no tumor left at the operation, Thompson says.

Treatment used to be more difficult for those with HER2-positive invasive cancers. Drugs such as Herceptin (trastuzumab) and Perjeta (pertuzumab) have been game changers, Anderson says. Some patients have evidence of a complete pathological response, meaning the absence of any detectable cancer on samples of affected breasts and lymph nodes. "Those are the patients we say we might not have to operate on," he says, though radiation would still be used. This approach is being verified in ongoing clinical trials but is not the current standard of care.

Women with invasive breast cancer typically get a sentinel lymph node biopsy, a procedure to remove the nodes to determine if cancer cells are present. It's usually done during lumpectomy or mastectomy to look for cancer spread. Experts don't recommend eliminating the procedure, because it helps with cancer staging and assessing the risk of disease recurrence based on the number of positive lymph nodes, George says.

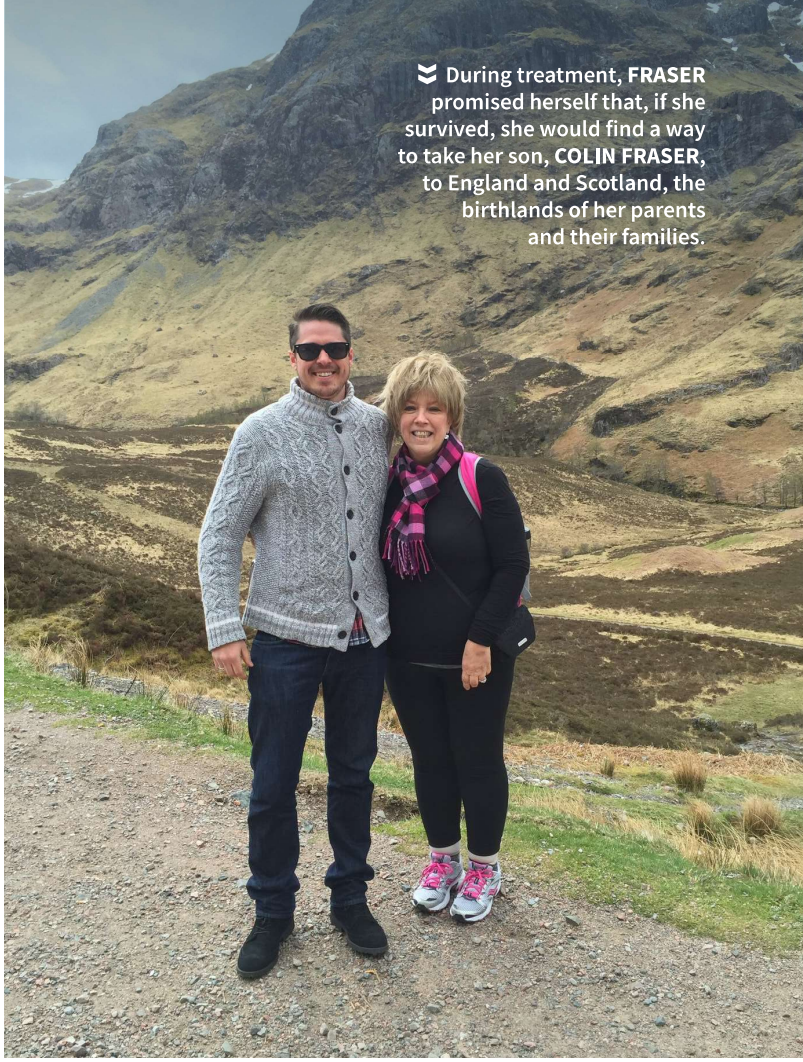
Currently, not all patients get axillary lymph node dissection, which removes anywhere from 10 to 40 lymph nodes. Lymphedema is a possible long-term side effect of lymph node surgery, affecting 20% to 30% of patients. Excess fluid buildup causes swelling, usually in the arms and legs but sometimes affecting other parts of the body. Patients with one or two positive nodes who had breast-conserving surgery will get radiation, so dissection may not be done, George says. If the patient did not respond to neoadjuvant systemic therapy and has positive node involvement, axillary lymph node dissection will be considered.

"The group we now struggle with is those with mastectomies and one or two positive sentinel nodes," says Dr. Lee Wilke, director of the breast center and a breast surgeon at University of Wisconsin Health in Madison, because these women may not all get radiation. "The question is, is it safe to not remove the axillary nodes?"

ASSESSING THERAPY'S RESPONSE

Without surgery, it is difficult to determine if all cancer cells are eliminated from the tumor bed. Imaging cannot detect everything, and needle biopsies can miss spots. "There is no strong agreement as to what is the best form of imaging and biopsy to give you a very accurate assessment," Thompson says. Leaving behind tumor cells is a missed opportunity to offer treatment that potentially protects against future cancer growth or spread.

Imaging might include mammogram, ultrasound, MRI or PET scans. Biopsies can be done with a small or big needle, with multiple passes necessary. "Bigger needles give a better idea of what's there, but these biopsies are not trivial things to go through," Thompson says, and there can be false negatives. At the moment, there's no gold standard for assessing whether any cancer remains.



During treatment, **FRASER** promised herself that, if she survived, she would find a way to take her son, **COLIN FRASER**, to England and Scotland, the birthlands of her parents and their families.

PHOTO PROVIDED BY VALERIE FRASER

"If we don't operate, we don't have a good way of knowing if everything is gone," he says.

Women with triple-negative breast cancer who experience a complete clinical response, with nothing seen in the breast or lymph nodes on biopsy, may in the future be advised to avoid surgery but still get radiation, Thompson says. At present, physicians still operate to prove nothing is left, he adds.

Liquid biopsy, which evaluates the blood for cancer cells, is approved for patients with stage 4 disease because the cancer has already spread. No liquid biopsy tests are approved for cancer stages 1 to 3 but are under active investigation to see if they can detect microscopic disease or predict who may have a higher chance of recurrence.

"The holy grail will be the ability to detect cancer cells in the blood and know whether there's evident cancer still remaining," Wilke says. Residual disease may or may not be seen in a liquid biopsy: "It's like looking for a needle in a haystack."

DECIDING ABOUT SURGERY

In 2007, Valerie Fraser learned she had two different cancers in the same breast: invasive ductal carcinoma and inflammatory breast cancer. Inflammatory breast cancer is rare, at 1% to 5% of all breast cancers. The diagnosis came after Fraser developed a quarter-size rash in her left breast, which eventually swelled, doubling in size, resulting in multiple workups. Her cancer was HER2 positive, and she was treated with Herceptin, followed by Herceptin and chemotherapy. After chemotherapy, her breast looked normal again, and imaging showed a complete response with no evidence of tumors. In spite of this, doctors recommended the normal treatment — surgery and radiation — to kill any remaining cancer cells. At that time, biopsies were not done to look for a pathological complete response, she says, though she would have considered that approach.

Like Pinto, Fraser spent a lot of time researching her disease. She says the risk of recurrence for inflammatory breast cancer is greatest in the first two years, and getting radiation and mastectomy after chemotherapy would have eliminated these options if the cancer recurred later. Therefore, she decided to proceed with careful monitoring. She also continued with Herceptin, and 13 years later has had no recurrence. Fraser went on to become a research advocate and, with her oncologist, founded the Inflammatory Breast Cancer International Consortium (ibcic.org) to bring researchers together throughout the world to advance the science, medicine and treatment options.

Avoiding surgery was not a hard decision, Fraser says, though she knows it's a psychologically difficult one for many women because they don't know if they had a pathological complete response to treatment. Clinical guidelines for surgical treatment of invasive breast cancer have not changed in recent years, and surgery is still recommended, Thompson says.

However, neither DCIS nor invasive breast cancer is one condition, Thompson says: "What we as a community tend to do is group people together and assume they're all the same." Treatment decisions must be individual, with patients and their doctors being mindful that evidence for subgroups in both cancer types can benefit from a specific approach rather than an across-the-board decision.

George has patients in their 80s and 90s who opted to forgo invasive breast cancer surgery. They may take hormonal therapy if appropriate and follow up more frequently. These older patients with early stage cancers are more likely to die from other causes, she says.

With shared decision-making, doctors review the risks and benefits of each approach, and the patient decides what to do. "As physicians, we work with patients to make sure they are comfortable with whatever approach they take. We don't have a crystal ball to know whether it's right or wrong," Wilke says.

Today, treatment is more personalized based on cancer type, stage, genetics, age and comorbidities. Twenty years ago, a conversation about breast cancer treatment would have taken her 30 minutes; now it can take an hour and a quarter or longer, Wilke says. "It's a lot to factor in," she says. "It's important for people to understand they have a lot of options."