Inflammatory Breast Cancer: Breast Cancer Without a Lump

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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Case Study

T.N. was a 45-year-old African American female who presented with right breast swelling, pain, skin changes, and redness for 2 weeks (Figure 1). She was initially treated with antibiotics for presumed mastitis by her primary care physician. When she did not respond to the antibiotics, a mammogram was ordered; it was negative except for enlarged axillary lymph nodes. She eventually had a skin biopsy that showed invasive ductal carcinoma, poorly differentiated, with dermal lymphatic invasion; the tumor was hormone receptor negative and HER2/*neu* negative. Based on her clinical presentation and pathology, she was diagnosed with inflammatory breast cancer. It is interesting to note that initial staging did not reveal metastatic disease.

T.N. was treated with neoadjuvant taxane- and anthracycline-based chemotherapy, but only had a minimal response to the chemotherapy. She was deemed not to be a good surgical candidate at that time, and restaging scans revealed new metastatic disease to the bone. She then proceeded with palliative radiation therapy to the breast and nodal basin (with concurrent capecitabine [Xeloda]), which had to be halted due to significant skin desquamation. While recovering from radiation, she developed new chest wall lesions both inside and outside of the radiation field, contralateral breast involvement, bilateral lymphadenopathy, and bilateral pleural effusions (Figure 2). She subsequently received one cycle of carboplatin and gemcitabine, but she was admitted to the hospital with severe chest wall pain and increasing pleural effusions before receiving a second cycle. Eleven months from the time of diagnosis, T.N. died of her disease.

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer. It accounts for 2% to 6% of all breast cancers and was once considered to be uniformly fatal with a 5-year survival rate of less than 5% (Woodward & Cristofanilli, 2009). With advances in radiation therapy, chemotherapy, and surgery, a multimodality approach is recommended and the survival rate has increased to over 40% for 5 years. In comparison, all breast cancers combined have a 5-year survival rate of almost 90% (Carkaci et al., 2009; Cristofanilli et al., 2007; Dawood et al., 2008a; Dawood et al., 2010b, 2010c; Mahon,

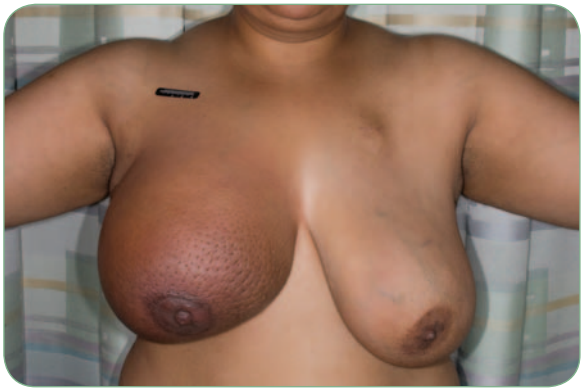

Figure 1. Initial photo of 45-year-old woman (T.N.) presenting with swelling, pain, skin changes, and redness of the right breast. Symptoms had persisted for 2 weeks.

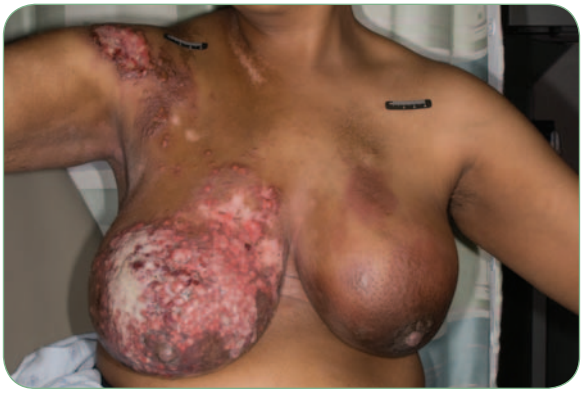

Figure 2. Photo of T.N. taken during her recovery from radiation—note development of contralateral breast involvement and bilateral lymphadenopathy.

2007). Epidemiologic information collected does not reveal obvious risk factors for the development of IBC with the exception that IBC patients tend to have a higher body mass index (Dawood et al., 2008a; Woodward & Cristofanilli, 2009).

Over the past decade, there seems to have been an increase in the incidence of IBC. Although the reason for the increase is not clear, it may be related to improved identification of IBC or increased use of breast imaging with mammography (Gonzalez-Angulo et al., 2007; Yang et al., 2009; Woodward & Cristofanilli, 2009). Inflammatory breast cancer is a disease that can develop in only a few days or weeks. It is frequently misdiagnosed, and patients are often metastatic at diagnosis. When reading about T.N.'s tragic story in the case study report at the beginning of this article, one might think it is an exception to the normal outcome of IBC. But sadly, T.N.'s experience is typical for this disease. The key to increased survival for this patient population is early identification of the symptoms of IBC, leading to early diagnosis and referral to health-care providers that specialize in treatment of this aggressive disease.

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Signs and Symptoms

As the case study illustrates, IBC tends to occur in a younger population, with a peak onset at the age of 50 (Gonzalez-Angulo et al., 2007) and a higher percentage of premenopausal patients (57% premenopausal vs. 42% postmenopausal) (Cristofanilli et al., 2007). One study demonstrated both a higher incidence of cases and poorer outcomes in the African American population (Yang et al., 2009; Woodward & Cristofanilli, 2009). There are several classic signs and symptoms of IBC, but it is important for advanced practitioners (APs) to note that not all the signs and symptoms are needed in order to make an IBC diagnosis (see Table 1 and Figures 3 through 5). There is a wide

Table 1. Classic Signs and Symptoms of IBC

- Breast erythema and edema
- Rapid breast enlargement—increase in size (up to 2 to 3 times the normal size) over a short period of time in an otherwise normal breast
- Tenderness
- Skin thickening
- Peau d'orange (looks like an orange peel)
- Warm to touch—generally not accompanied by fever
- A distinct mass may not always be felt
- Breast pain

variety of ways IBC can present, and it is easy to see why it is often confused with mastitis as similar signs and symptoms occur with both conditions. While pathologic confirmation of invasive cancer is the first step in the diagnostic process, the clinical symptoms described in Table 1 confirm the diagnosis as IBC. For this reason, a good history of symptoms is essential to a proper diagnosis.

Diagnosis and Staging

BREAST IMAGING

There are several different types of breast imaging that assist in identifying the extent of disease, evaluating the locoregional lymph nodes, and guiding the location for biopsies. A mammogram may show skin thickening, diffuse increased density, trabecular and stromal thickening, or architectural distortion, or in some cases it may be completely normal (Iniesta, Mooney, & Merajver, 2009; Cristofanilli et al., 2007; Dawood et al., 2010b; Sinclair & Swain, 2010; Yang, 2009). A distinct mass is not always identified, but if there is a mass it tends to be irregular and solid with ill-defined margins (Yang, 2009).

Ultrasound can further define and visualize any focal masses seen in the breast and the nodal basin, including axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes. In order to accurately stage the disease, ultrasound can be used to guide the selection of appropriate biopsy sites. It is not uncommon to see the lymph nodes involved with metastatic disease on initial presentation in up to 83% to 96% of patients (Bristol et al., 2008; Carbognin et al., 2009; Carkaci et al., 2009; Yang, 2009; Singletary & Cristofanilli, 2008). In my practice, a patient with IBC presented to the clinic with only a 10-day history of symptoms, but she already had axillary, infraclavicular, supraclavicular, and internal mammary lymph nodes involved with metastatic disease.

An MRI of the breast may further identify any underlying masses or architectural distortion, measure the skin thickness, and evaluate axillary and internal mammary adenopathy (Carbognin et al., 2009). An MRI can also assist the surgeon in determining how extensive the surgery needs to be (Figure 6).

UNIQUE PATHOLOGY

Although IBC is a clinical diagnosis, there are trends seen in the pathology that are classic for IBC and help to further delineate this disease as a unique breast cancer. The most common pathologic type is invasive ductal carcinoma; typically it is poorly differentiated, and exhibits

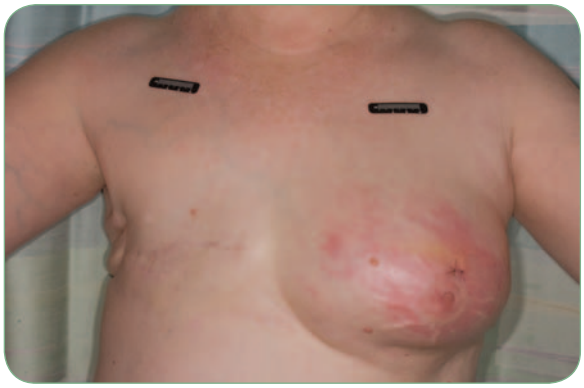

Figure 3. Presenting photo of woman with erythema, pain, and edema. She had a history of prior contralateral breast cancers. Staging scans revealed widespread metastatic disease.

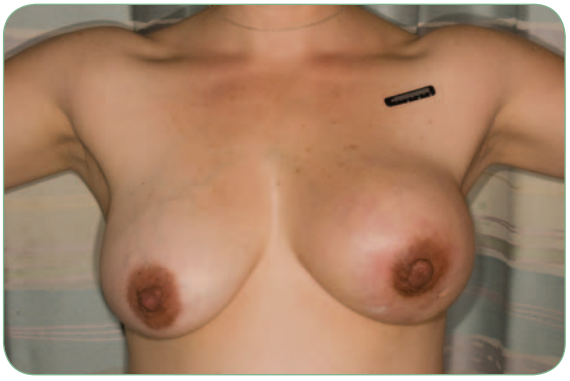

Figure 4. Presenting photo of woman with 3-month history of erythema, pain, and edema. Staging scan revealed metastatic disease to the bone.

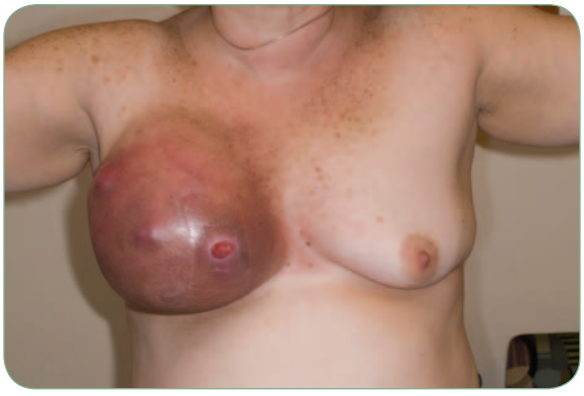

Figure 5. Presenting photo of woman with 5-month history of erythema, pain, ulcerations to the breast, and edema.

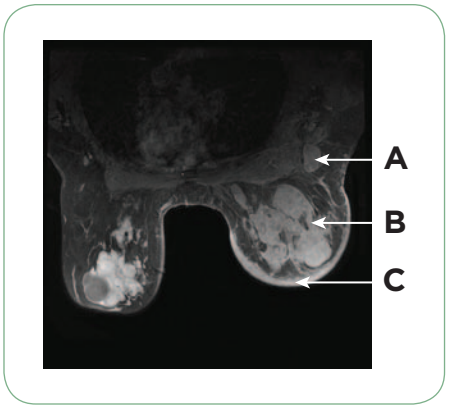

Figure 6. Breast MRI that shows axillary adenopathy (A), increased density (B), and diffuse skin thickening (C).

lymphovascular invasion vs. non-IBC, which tends to have a higher percentage of tumors that are well differentiated without lymphovascular invasion (Carkaci et al., 2009; Cristofanilli et al., 2007; Dawood et al., 2010b; Hance, Anderson, Devesa, Young, & Levine, 2005; Woodward & Cristofanilli, 2009). Another unique feature of IBC is the presence of tumor emboli in the dermal lymphatics. Basically, tumor cells block the lymphatic channels and are the cause of the classic symptoms of breast enlargement and erythema seen in patients with IBC (Mahon, 2007; Sutherland, Ashley, Walsh, Smith, & Johnston, 2010; Woodward & Cristofanilli, 2009). Although tumor emboli are not unique to IBC, they are infrequently seen in non-IBC breast cancer (Iniesta et al., 2009).

Hormone receptor status and HER2/*neu* status also tend to be different in IBC vs. non-IBC. According to the American Cancer Society (2010), only 10% to 20% of breast cancers are triple negative (estrogen receptor [ER], progesterone receptor [PR], and HER2/*neu* negative), but almost twice as many patients with IBC (36%) are triple negative (Dawood et al., 2010c). Some studies show that up to 83% of IBC tumors are ER negative; the lack of hormone receptor expression has been associated with a more aggressive clinical course and overall decreased survival (Dawood et al., 2010c). HER2/*neu* is overexpressed in approximately 20% of non-IBC breast cancers, but in IBC, HER2/*neu* is overexpressed in 38% to 52% (Dawood et al., 2008a; Iniesta et al., 2009).

Staging Workup

It is important to properly stage patients with IBC because over 40% will have distant metastases on presentation (Carkaci et al., 2009; Dawood et al., 2010c; Yang, 2009). PET/CT scan can be advantageous in identifying the metabolic activity of a tumor in this disease and in detecting metastatic disease not evident in standard imaging. Typically, PET/CT scan will identify increased metabolic activity within the affected breast and the skin thickening will be apparent (Yang, 2009). In a retrospective study, Carkaci et al. (2009) found that 22% of the patients with IBC had metastatic disease to the bone on presentation as identified by PET/CT. Nuclear bone scan did not accurately diagnose the metastatic disease to the bone in 33% of these patients. In addition, 17% of patients were upstaged due to positive PET/CT scans.

Management

CHEMOTHERAPY

Due to the extent of disease upon presentation, the breast is usually considered inoperable at the time of presentation. Neoadjuvant chemotherapy is needed to downstage the disease and treat possible micrometastatic disease (Carkaci et al., 2009; Dawood et al., 2010a; Yang, 2009). The goal is to achieve a pathologic complete response at the time of surgery, which is a good prognostic indicator of both overall and disease-free survival (Fleming et al., 1997; Mahon, 2007; Damast et al., 2010; Cristofanilli, Buzdar, & Hortobagyi, 2003; Giordano & Hortobagyi, 2003; Bristol et al., 2008; Iniesta et al., 2009; Perez et al, 1994). In other words, less disease present at the time of surgery predicts an improvement in overall outcome and survival. Anthracycline- and taxane-based regimens are the most effective chemotherapy treatments for IBC (Sinclair & Cristofanilli, 2010; Sutherland et al., 2010).

The overexpression of HER2/*neu* is associated with higher recurrence rates and reduced survival (Sinclair & Swain, 2010). Therefore, in patients with nonmetastatic disease and tumors that overexpress HER2/*neu*, trastuzumab (Herceptin) should be added to their neoadjuvant chemotherapy and continued until 1 year of therapy has been completed (Dawood et al., 2010a). The National Comprehensive Cancer Network (NCCN) treatment guidelines (2011) recommend

trastuzumab be given, except during anthracycline-based therapy, continuing for 1 year. The American College of Surgeons Oncology Group currently has a phase III study (ACOSOG Z1041) looking at the safety and efficacy of using trastuzumab concurrently with FEC-75 (fluorouracil, epirubicin, cyclophosphamide); preliminary results have shown no increase in grade 3/4 toxicity or cardiac dysfunction with FEC-75 plus trastuzumab (Buzdar et al., 2009). Trastuzumab-based regimens are active and bring about a higher rate of complete pathologic response, but unfortunately a high recurrence rate is still seen (Dawood et al., 2010a).

Clinically, practitioners tend to see an improvement in the breast within 1 to 2 weeks combined with a significant reduction in discomfort. Unfortunately, a considerable number of patients progress during neoadjuvant chemotherapy (5%–20%) (Iniesta et al., 2009). It is not uncommon to have a patient initially respond clinically to therapy and then exhibit progression of disease in the breast before completion of therapy. In this case, clinicians need to promptly change therapies in order to minimize the exposure to an ineffective regimen and, ideally, get the patient on a more effective treatment. Again, the goal in nonmetastatic patients with IBC is to reduce the extent of disease to increase chances of survival.

SURGERY

Mastectomy may further reduce the risk of recurrence (Fleming et al., 1997). As it is difficult to judge the extent of residual disease after neoadjuvant chemotherapy for IBC, even with imaging, breast-conserving surgery is not an option. Typically there is no distinct mass or area to excise, which also makes breast-conserving surgery impossible. Additionally, since there tends to be dermal lymphatic involvement with this disease, skin-sparing mastectomies are not recommended because tumor cells could easily be left behind (Dawood et al., 2010b). Reconstruction is best if it is delayed for up to 2 years due to the high local recurrence rate.

Since most patients already have axillary lymph nodes involved, sentinel lymph node sampling is not an option and an axillary lymph node dissection is necessary. It is theorized that since IBC involves the dermis and lymphatics, there may be an occlusion in the lymphatic channels, making it difficult to identify the sentinel lymph nodes. Additionally, Stearns et al. (2002) found that sentinel lymph node biopsy produced a high false-negative result and may be unsuccessful as well.

RADIATION THERAPY

Radiation therapy is often used to achieve better local control, demonstrating a 5-year locoregional control rate of 87% in one series with distant metastases remaining a challenge in 47% of patients with IBC (Bristol et al., 2008; Damast et al., 2010). In an effort to offset the high proliferation rate of IBC in patients with poor surgical outcome (extensive residual disease, close surgical margins, or under 45 years of age), accelerated hyperfractionated radiation therapy (given twice daily) and high doses of radiation (66 Gy) are being used in practice (Dawood et al., 2010b). Accelerated hyperfractionated radiation therapy is an aggressive approach associated with an increase in grade 3/4 toxicities, so it should be reserved for those with poorer prognostic factors for optimal local control.

HORMONAL THERAPY

The use of adjuvant hormonal therapy is standard in non-IBC breast cancer and should also be considered standard in IBC. Although there are no studies looking specifically at patients with IBC and adjuvant hormonal therapy, patients with hormone receptor–positive tumors should be treated, according to the same guidelines, with tamoxifen or an aromatase inhibitor as indicated according to menopausal status (Iniesta et al., 2009).

Metastatic and Recurrent Disease

Unfortunately, IBC is associated with a 5-year recurrence rate of almost 65%, with visceral, local soft-tissue, bone, and distant soft-tissue recurrences most common (i.e., lymph nodes, contralateral chest wall, etc.) (Cristofanill et al., 2007). The extent of residual disease after neoadjuvant chemotherapy, including the number of positive axillary lymph nodes, has been shown to predict higher recurrence rates. According to Bristol et al. (2008), 5-year survival rates for patients achieving complete pathologic response, partial response, and less than partial response were 73%, 51%, and 12%, respectively.

Recent studies have suggested a higher incidence of brain metastases in patients with IBC, with a median survival of only 6 months (Dawood

et al., 2010c). In one study, the 1-year recurrence rate of brain metastases was 2.7%, with a 2-year recurrence rate of 18.7%. The overall rate of recurrence in the brain was 15.8%, with a median time to development of brain metastases of 19 months. Tumor characteristics predicting a higher incidence of metastasis to the brain include triple-negative tumors (ER negative, PR negative, and HER2 negative), diagnosis of metastatic disease at presentation, and HER2-positive disease. Patients who were diagnosed with stage III disease at presentation and subsequently developed brain metastases had a poorer survival rate than those patients initially diagnosed with metastatic disease on presentation (4-month vs. 6-month survival rate).

Although not reported in studies, our clinical experience demonstrates that there appear to be differences in the presentation of brain metastases for some patients. Interestingly, these patients seem to be minimally symptomatic at presentation. Early in the development of our IBC clinic, we annually screened patients and found several women with multiple brain metastases who were asymptomatic and still more with only slight headaches relieved by acetaminophen. As a result of our experience, the threshold for getting an MRI of the brain for minimally symptomatic headaches should be lowered.

Figure 7 shows the brain MRI of a woman with IBC who only complained of a headache when she received antiemetics after chemotherapy. She was asymptomatic for the remainder of the chemotherapy cycle (more than 2 weeks), until 2 days prior to receiving the next cycle. At that time, she reported a slight headache and family members noted that she seemed a little different but there was no clear symptom they could point out. She did not complain of nausea, vomiting, or gait disturbances, and clinically she did not exhibit neurologic defects. Hours before her MRI, she had a grand mal seizure and was admitted to the hospital; she expired 5 days later.

Implications for Advanced Practitioners

INITIAL WORKUP, PORT PLACEMENT, AND CARDIAC WORKUP

Prior to starting therapy, a baseline photograph of the affected breast and its relationship to the unaffected breast should be obtained. Inflammatory breast cancer is a visual disease that can change quickly. Changes in the breast can be expected to be seen in as little as 1 to 2 weeks.

Since patients will be receiving weekly chemotherapy requiring the placement of numerous IVs, a port is recommended for better vascular access. Additionally, they will most likely be receiving anthracycline-based chemotherapy, and a port can help avoid extravasations.

All patients should have a baseline cardiac evaluation as they will be receiving anthracycline-based therapy. If a patient's tumor is HER2/*neu* amplified, trastuzumab will be added to her regime and frequent cardiac monitoring is necessary.

MONITORING RESPONSE TO THERAPY

Frequent monitoring of response to therapy is extremely important. Advanced practitioners should be aware that it is not uncommon for patients with IBC to suddenly progress almost overnight despite initially responding to therapy. Also important is analgesia for breast pain early in the treatment course. The need for pain medications generally decreases after the first week or two as response to therapy occurs. As for most patients receiving chemotherapy, laboratory values should be monitored for toxicity per institutional guidelines.

GENETIC COUNSELING REFERRAL

Approximately 10% of all breast cancers are related to a hereditary predisposition. A thorough family history may give you an indication of possible inherited genetic mutations (Mahon, 2007); see Table 2. Inflammatory breast cancer gener-

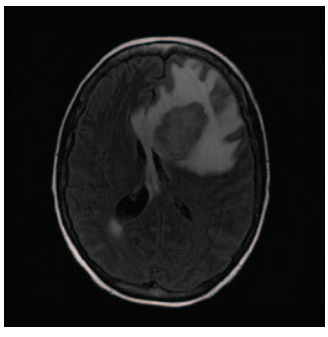

Figure 7. Brain MRI of woman with IBC who only complained of a headache when she received antiemetics after chemotherapy.

ally occurs at a younger age, and there may be a higher incidence of inherited genetic mutations seen in this population. It may be interesting to note that our experience has not shown this to be true. But despite our experience, patients should be sent for genetic counseling if appropriate.

LONG-TERM FOLLOW-UP

Like non-IBC breast cancers, routine follow-up screening scans without evidence of recurrence are not recommended. Patients should be educated to report persistent symptoms of pain or acute changes to their health-care provider, who should perform appropriate studies to evaluate. In our practice, we typically use the 2-week rule: if there are persistent symptoms for 2 weeks, the patient should be evaluated.

After having seen several hundred patients with IBC, our IBC group of medical oncologists, radiation oncologists, radiologists, surgeons, and nurse practitioners convened to establish long-term follow-up guidelines. Table 3 illustrates the follow-up guidelines we established for patients with IBC. In agreement with the NCCN Guidelines (2011), we do not recommend routine use of PET/CT scan or CT scan for surveillance.

Discussion

Inflammatory breast cancer is a rare but aggressive disease with a poor prognosis. As the case study illustrates, IBC presents a difficult challenge to practitioners due to its aggressiveness and changing clinical behavior. It needs to be identified quickly and treated aggressively with anthracycline- and taxane-based chemotherapy followed by surgery and radiation therapy. Clearly, achieving a pathologic complete response with neoadjuvant chemotherapy is the best hope these patients have to increase their chances for survival. Clinicians need to be diligent in their management of this unique population with frequent monitoring and investigation of acute changes. Upon diagnosis, patients with IBC need to be referred to a specialty center with experience with the management of IBC. After that, patients can easily be managed by their local providers under the guidance of an IBC treatment specialist.

DISCLOSURE

The author has no conflicts of interest to disclose.

Table 2. Possible Indicators of Inherited Genetic Mutations

- Several relatives with breast and/or ovarian cancer
- Cancers are diagnosed at an age that is younger than that seen in the general population
- Cancer is seen in more than one generation
- Relative with bilateral breast cancer
- Ashkenazi Jewish heritage
- History of male breast cancer in the family

Table 3. Long-Term Follow-Up for Patients With Inflammatory Breast Cancer

Clinical exam:

- Every 3 months x 2 years
- Every 6 months x 6 months
- Then annually

Imaging and labs:

- Routine labs per institutional guidelines on every visit
- Annual mammogram on contralateral breast
- If age at diagnosis was less than 40 years, alternate breast MRI with mammogram so patients will get breast imaging every 6 months x 2 years

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