A Woman With Primary Breast Cancer and a Solitary Sternal Metastasis

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By Alexander Menter, MD [1], Alexander Urquhart, MD [2], Virginia F. Borges, MD, MMSc [3], Rachel A. Rabinovitch, MD [4], Meenakshi Singh, MD [5], William Robinson, MD, PhD [6], Paul Seligman, MD [7], Christina A. Finlayson, MD [8], and Anthony D. Elias, MD [9]

The patient presented to her primary care physician 3 months prior with an inverted left nipple and a palpable lump that was highly suggestive of neoplasm on mammogram. An ultrasound-guided core biopsy revealed an infiltrating solid-type ductal carcinoma in situ. The estimated size of the mass was approximately 1 cm. She had no symptoms suggestive of metastatic disease.

The patient is a 42-year-old premenopausal female who presents with a new diagnosis of breast cancer to our multidisciplinary second opinion clinic.

History

The patient presented to her primary care physician 3 months prior with an inverted left nipple and a palpable lump that was highly suggestive of neoplasm on mammogram. An ultrasound-guided core biopsy revealed an infiltrating solid-type ductal carcinoma in situ. The estimated size of the mass was approximately 1 cm. She had no symptoms suggestive of metastatic disease.

CT and PET Images From the Time of Original Diagnosis

The patient requested CT/PET imaging as part of her preoperative evaluation. This scan revealed a metabolically active lytic lesion in the manubrium of the sternum (Figure 1). Several different radiologists were consulted, and opinions differed as to whether or not this likely represented a metastatic lesion. After reviewing the case with several radiologists, the surgeon chose to proceed with definitive surgery and monitor the sternal lesion.

The patient elected to undergo bilateral mastectomies with immediate reconstruction. Pathology from the mastectomy specimens revealed a 1.1-cm left infiltrating ductal carcinoma, combined histologic grade 2. There was no vascular or lymphatic invasion. Six sentinel lymph nodes were examined and found to be free of tumor on H and E (hematoxylin and eosin) stains and cytokeratin immunostaining. The tumor was stained for estrogen and progesterone receptors, which demonstrated 58% estrogen-receptor positivity, 3% progesterone-receptor positivity, and Ki-67 staining of 13%. HER2/neu fluorescence in situ hybridization analysis revealed HER2 amplification of 7.0. The patient's right prophylactic mastectomy revealed atypical hyperplasia.

Postoperatively, the patient saw a medical oncologist in town. The medical oncologist reviewed the workup and elected to obtain a fine-needle aspirate of the sternal lesion prior to finalizing recommendations for adjuvant therapy. The fine-needle aspirate of the sternal lesion demonstrated metastatic adenocarcinoma consistent with a breast primary. After discussing a variety of treatment options with the primary oncologist, the patient presents to the University of Colorado Breast Cancer Program for a second opinion.

The patient has no other significant past medical history. The patient is G2 P2, with menarche at age 12 and ongoing regular menses. She bore her first child at age 32 and breast-fed both of her children. She is a former smoker and drinks alcohol socially. There is no family history of breast, ovarian, or prostate cancer.

Discussion

Dr. William Robinson: Why would anyone with a stage I breast cancer get staging scans?

Dr. Alexander Menter: National Comprehensive Cancer Center guidelines suggest that screening with bone scans...
or abdominal imaging should be optional for patients with stage IIA and IIB disease and recommended for patients with stage III or greater disease.[1] These recommendations are based on data showing that the incidence of asymptomatic but detectable metastatic disease in women with early-stage breast cancer is related to stage of disease. In a review of the literature, bone scans detected skeletal metastases in 0.5%, 2.4%, and 8.3% of women with stage I, II, and III disease.[2] In the same Canadian review, ultrasonography detected hepatic metastases in 0% of patients with stage I disease, 0.4% with stage II, and 2.0% with stage III. False-positive rates ranged from 10% to 22% for bone scanning and 33% to 66% for liver ultrasound. The false-negative rate for bone scanning was about 10%. 

Dr. Paul Seligman: I looked at this a few months ago and was amazed at how little there was on the performance of CT scans. They are probably more sensitive and specific than a liver ultrasound, but there is not much published on the performance of CT scans in the setting of localized breast cancer. One study from Stanford University reviewed abnormalities on CTs obtained for radiation treatment planning, demonstrating that 11% of studies had abnormalities with 3% of studies demonstrating unexpected metastatic foci.[3] Unfortunately, the cancer stage of these patients was not reported, so no one knows what to do with the results.

Dr. Robinson: It's the false-positive scans that wear you down over the long run. The patients with false-negative scans may eventually wind up receiving overly aggressive therapy, but they are probably still benefiting from the treatment. The biopsies and scans necessary to track down the false-positives drive you up the wall.

Dr. Menter: I wonder whether some community doctors are doing more scans in patients with HER2/neu-positive or high-grade disease. HER2/neu overexpression clearly increases risk of relapse in women with node-positive disease, but the prognostic significance is weaker in women with node-negative breast cancer.[4-6] Women with node-negative breast cancers that are high-grade lesions or high Oncotype DX scores clearly are at higher risk for relapse than their low-grade/low-score counterparts, but it hasn't been examined prospectively whether this results in a higher yield on screening scans.

In the absence of data, I think it is reasonable to obtain scans on patients with borderline lesions based on stage, but also on worrisome prognostic markers, as these adverse markers would logically increase the yield of finding unexpected metastatic lesions. However, in this case, I would not have considered her tumor high risk except for the HER2/neu status, and would not have recommended screening scans unless she had some hint of localizing symptoms in her prior history.

**Screening Options**

Dr. Seligman: What is the relative sensitivity of PET/CT fusion scans compared to contrast CT and bone scans for staging local breast cancers?

Dr. Alexander Urquhart: While there are some reports of the usefulness of PET/CT in cancer, there are limited reports specifically looking at preoperative staging in breast cancer and especially comparing it to standard modalities such as CT and bone scans. Tatsumi et al retrospectively reviewed PET/CT on 75 patients with known breast cancer and compared the PET/CT images to the CT findings alone. PET/CT accurately staged 86% of patients; CT accurately staged 77% of the patients. They concluded that PET/CT added incremental diagnostic confidence to PET in more than 50% of patients, and detected more regions with malignant lesions than CT alone.[7] In this study they did not use separate CT images; this is a weakness in the study that also points out a weakness in the diagnostic accuracy of PET/CT. The fused CT images do not include contrast, and therefore are less accurate than standard contrast-enhanced staging studies. There are more robust data looking at FDG/PET alone.

A recent meta-analysis of FDG/PET in breast cancer reveals a sensitivity of 90% with a false-positive rate of 12%.[8] Straight PET also demonstrates a higher sensitivity and specificity to detect recurrence of metastasis when compared to conventional imaging studies (CT, MRI, bone scan).[9] In regard to comparing PET/CT to bone scan this is a bit more difficult. In a prospective trial of 57 breast cancer patients, FDG/PET produced more false-negative findings for bone metastasis than other sites. This is thought to be due to poor uptake of FDG by bone. Interestingly, the false-positive cases were related to inflamed tissue, blood pooling, and bowel,[10] pitfalls that could be clarified by fusion CT. FDG/PET is probably more sensitive in detecting osteolytic or marrow lesions and less sensitive in detecting osteoblastic lesions.[11] 

Dr. Seligman: The bottom line is that there isn't much in the literature to justify using PET/CT for screening, but it seems like we are seeing a lot of these PET/CT scans for second opinions. I don't know what that means, but I hope some better data come out soon.

Dr. Virginia Burnes: Dr. Finlayson, would you have proceeded with surgery without a biopsy of the lesion in

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A thorough approach to preoperative staging would necessitate the complete evaluation of any suspicious clinical or radiologic findings prior to embarking on surgical therapy. These important endpoints are pursued primarily when they will make a difference in clinical treatment planning. In this case, perhaps the patient would have elected breast conservation rather than mastectomy if she had known her true pathologic stage. In addition, the primary tumor provides an excellent marker of treatment response if it is left in situ for initial chemo/hormonal therapy.

Dr. Rabinovitch: What if you knew she had stage IV disease?

Dr. Urquhart: The role of surgery in patients presenting with stage IV breast cancer is providing a benefit in local control; there are some studies suggesting a long-term survival benefit as well.[12] A review of the National Cancer Data Base identified over 16,000 women with stage IV disease at diagnosis. In this retrospective analysis, 43% had no definitive local surgery and 57% had resection of the primary tumor. Of those having local surgery, 38% had lumpectomy and 57% had mastectomy. The 3-year survival for no definitive surgery, lumpectomy, and mastectomy was 17%, 28%, and 32%, respectively. Local surgical treatment was an independent significant variable even when controlled for use of systemic therapy, number of metastases, and type of metastases. Looking retrospectively, it would have been ideal for the staging to be complete prior to surgery. A treatment response to initial systemic therapy could have been assessed. The patient may have elected a less aggressive procedure but I agree with the pursuit of definitive local control for both optimum palliation and the possibility of a survival benefit as well.

Dr. Master: Do you find that more women are choosing to opt for bilateral mastectomies with immediate reconstruction?

Dr. Finlayson: There are many factors that come into play when looking at rates of mastectomy vs breast conservation. These include geographic location, characteristics of the operating surgeon, and the preoperative counseling experience of the patient. In my experience, when women have the option of breast conservation, 19% elected unilateral or bilateral mastectomy.[13] Of the women who chose mastectomy, 28% also chose reconstruction. For the women who required mastectomy, 25% chose immediate reconstruction. All of these women were offered and encouraged to consult with a plastic surgeon prior to mastectomy. I think more women are taking the time and initiative to become more educated about their treatment options. With this improved education I find there is a better match between an individual patient’s treatment goals and objectives and the actual surgery performed.

Previously, I think that a common assumption had been that the more women understand their surgical options and participate in treatment planning, the more they would choose lumpectomy. Somewhat surprisingly, a recent survey of women with a recent diagnosis of breast cancer in Los Angeles and Detroit demonstrated that patients with more input into their surgical decision-making were more likely to choose mastectomy.[14] As to why women chose more aggressive surgery, it seemed largely due to concerns about the risk of recurrence and the attendant risks and inconveniences of radiation treatment.

Dr. Robinson: Was this sternal lytic lesion a direct extension of her primary tumor, a hematogenous metastasis, or an extension of an internal mammary node?

Dr. Menter: Since the margins of the mastectomy specimen were free of tumor, the sternal lesion represents a metastasis of the breast carcinoma.

Dr. Borges: What's the likelihood of sterilizing this lesion with radiation?

Dr. Rabinovitch: First, for clarity, it needs to be said that in 99% of cases the goal of radiation is to provide palliation—either to treat pain or prevent an impending fracture. For this reason, we are typically able to give shorter courses of treatment aiming for 20 to 30 Gy, or even single fractionated doses of 8 Gy. Several studies now have shown that the palliative benefits of radiation to bony metastases are equivalent with shorter courses of radiation treatment.[15,16] We don't think that smaller doses and shorter courses of radiation will result in a high rate of "sterilization" of the tumor bed, but we do it anyway because 99% of the time, the goal of treatment is palliation, and most patients are unlikely to live long enough to experience a symptomatic recurrence in the same area. If someone were to specifically ask me for my best shot at "sterilizing" this sternal lesion in the hopes of achieving a long-term remission or cure, I would probably treat to a higher total dose—say 45 to 50 Gy—and treat over a longer period—say 4 to 6 weeks—since the smaller fraction dose will result in fewer long-term radiation complications. There is no way to guarantee whether this will result in temporary or permanent control of the tumor in this area. It's all guesswork, but "sterilization" probably has more to do with how well she responds to her primary chemotherapy than the radiation.

Dr. Uppal: What about her implants?
Clearly, despite using intensity-modulated radiotherapy with CT planning, her implants will get some radiation and there will be some risk of a poor cosmetic outcome—and that needs to be part of her decision-making when weighing the pros and cons of aggressive treatment. But because we aren’t treating her whole chest wall, I would predict that the risk of a poor outcome with the implant would be much less than we would normally estimate for women needing chest wall radiation with implants in place.

**Aggressive Chemotherapy**

**Dr. Borges:** So, what is the literature on aggressive chemotherapy for oligometastatic breast cancer? Is there a good reason to put this poor woman through that much treatment and toxicity?

**Dr. Anthony Elias:** Questions about stage IV disease and long-term survival generally start with a review of the case series from MD Anderson looking at long-term survival in patients achieving a complete response (CR) to front-line anthracycline and alkylating therapy.[17] In this study, 1,581 patients treated at MD Anderson on consecutive doxorubicin and alkylating agent-containing protocols between 1973 and 1982 were retrospectively reviewed to assess characteristics of long-term survivors. From this group, 17% achieved initial CRs and 3% remained in CR for more than 5 years. After more than 15 years of follow-up, 26 patients remain in first CR, with four patients dying in CR. The long-term CR group had more premenopausal patients, a younger median age, a lower tumor burden, and better performance status. Although data from MD Anderson are difficult to duplicate in the "real world," this study does demonstrate a small but real proportion of women with metastatic breast cancer in whom "cure" is possible with chemotherapy alone.

As far as oligometastatic disease is concerned, some of the best data come from studies utilizing high-dose chemotherapy and stem-cell transplant. In one study from our institution, 60 patients with minimal metastatic disease amenable to local therapy were treated with resection and high-dose chemotherapy with stem-cell rescue.[18] After 5 years of follow-up, 5-year relapse-free and overall survival rates were 52% and 62%, respectively. HER2/neu expression, number of tumor sites, primary axillary nodal ratio (number of positive nodes divided by number of sampled nodes), number of positive axillary nodes, and delivery or omission of radiotherapy to metastases correlated with relapse-free survival. While these were certainly highly selected patients, it demonstrates that with aggressive, multimodality therapy, a large portion of women with resectable metastatic lesions can have prolonged disease-free survival, some of which may eventually fit a definition of "cure." A similar German study showed that 27% of the 40 patients treated with surgery and high-dose chemotherapy were progression-free after 5 years.[19]

**Dr. Anthony Elias:** But you are quoting data from the stem-cell transplant literature which generally dead patients, or at least those on life support and moribund in the ICU.

**Dr. Robinson:** The rate of complete remission in these studies was very high with the use of high-dose chemotherapy and stem-cell rescue, so one could argue that conventional chemotherapy regimens would be unlikely to provide any semblance of similar benefit.

But for HER2/neu-amplified patients, neoadjuvant trastuzumab (Herceptin)-based combination regimens are achieving 47% to 65% pathologic CR rates before throwing in the potential benefits of surgical resection or focused radiation to oligometastatic disease.[20-22] Although there is plenty of room for the debate over the magnitude of benefit in real world situations, I believe there are sufficient data to offer the option of aggressive, multimodality therapy to those patients willing to trade toxicity for the rare prolonged disease-free survival or cure.

**Dr. Seligman:** So what does everyone think about ovarian suppression and treatment with an aromatase inhibitor compared to tamoxifen?

**Dr. Anthony Elias:** There are data in the premenopausal setting on the enhanced benefit for tamoxifen with ovarian ablation over tamoxifen alone in the setting of metastatic disease, and combination endocrine therapy would be considered a standard option. In postmenopausal women, there are data to support the use of an aromatase inhibitor over tamoxifen regardless of HER2/neu status,[23-25] and the next logical investigation is whether chemical ovarian ablation is an adequate form of menopause to allow a premenopausal woman to safely take an aromatase inhibitor and derive the same enhanced benefit. Several randomized phase III studies ongoing in early-stage breast cancer, such as the TEXT, SOFT, and ASBCG 12 clinical trials, should provide definitive answers to this question. However, given this woman’s metastatic presentation with hormone receptor-positive disease, we really do not want her to continue having ovarian estrogen production, so I would advocate for oophorectomy to remove any question of menopausal status and then treat with an aromatase inhibitor. This also allows us to
address the issue of tamoxifen resistance in HER2/neu-positive breast cancer[26] and utilize the antiendocrine treatment that is currently preferred in HER2/neu-positive disease based on several lines of evidence to say that there is less innate resistance to aromatase inhibitors.[27-29]

Systemic Therapy Recommendations

Dr. Menter: What systemic therapy would you recommend? Hormone therapy alone? Chemotherapy followed by hormone therapy?

Dr. Seligman: I would initially choose hormone therapy. Since tumors that are HER2/neu-positive are somewhat tamoxifen resistant, I would advocate for ovarian oblation and treatment with an aromatase inhibitor.

Dr. Urquhart: I would probably choose antihormonal therapy, using an aromatase inhibitor in combination with GHRH analog. She has a single site of metastatic disease and is asymptomatic, so it makes sense to me to treat her with a low-toxicity, but effective regimen. I think there are enough data to support the use of aromatase inhibitors over tamoxifen in this setting (HER2/neu positive), even though the ASCO guidelines suggest that the existing data are insufficient to use biomarkers to guide therapy choice. You could consider the addition of trastuzumab as well, but this has not been as well studied.

Dr. Urquhart: Although this patient has metastatic disease, it is limited and she is young. I would be quite aggressive in her therapy beginning with doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide chemotherapy followed by paclitaxel and trastuzumab, local radiation therapy, zolendronic acid (Zometa) and then antihormone therapy starting with tamoxifen.

Dr. Robinson: Although this patient has metastatic disease, it is limited and she is young. I would be quite aggressive in her therapy beginning with doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide chemotherapy followed by paclitaxel and trastuzumab, local radiation therapy. I would treat her with a regimen similar to the N9831 trastuzumab arm with AC followed by weekly paclitaxel and trastuzumab. Although I know the cosmesis of her implant is at risk, I would advocate for radiation to her sternal metastasis with "curative" intent. After that I would recommend tamoxifen, and an eventual switch to an aromatase inhibitor when menses cease.

Dr. Borges: I would complete further staging evaluation with a diagnostic quality CT scan of the chest, abdomen, and pelvis with contrast and a nuclear bone scan. If the metastasis to her sternum is the only true evidence of disease, I would radiate it and place her on antiendocrine therapy. Ideally, I would prefer to offer a patient in this circumstance a clinical protocol. But in this case, the removal of the breast removed her only measurable disease, so the RECIST criteria would not allow this patient onto most protocols at present. Therefore, I would proceed with combined endocrine therapy involving surgical oophorectomy and an aromatase inhibitor.

One unclear area is when to incorporate the use of trastuzumab for this woman. The addition of trastuzumab to chemotherapy has shown benefit with improved response rates, time to progression, and overall survival when compared to chemotherapy alone, and clearly one would incorporate trastuzumab at the time of initiating chemotherapy. A phase II study in advanced disease of trastuzumab with letrozole (Femara) in estrogen and progesterone receptor-positive, HER2/neu-positive patients reported 30 evaluable patients with an overall response rate of 27%, clinical benefit rate of 54%, median duration of response of 72 weeks, and median time to progression of 35 weeks.[30] Whether the combination of trastuzumab and aromatase therapy would be of significant benefit over an aromatase inhibitor alone in enhancing response, duration of response, and survival is the subject of ongoing research.

Follow-up

FIGURE 2

PET/CT Images Obtained at the Completion of AC Chemotherapy and 12 wk of Paclitaxel With Herceptin

After discussing the pros, cons, and unknown aspects of aggressive multi-modality therapy, the patient elected to pursue an aggressive approach. She has completed four cycles of doxorubicin/cyclophosphamide chemotherapy and 12 weeks of weekly paclitaxel with trastuzumab. She is on maintenance trastuzumab and has completed radiotherapy to her sternal metastasis. A
repeat staging PET/CT scan after the chemotherapy but before radiation showed no new metastatic lesions and a dramatic decrease in the PET uptake in her sternal lesion (Figure 2). She has tolerated her treatment well thus far with no severe or unexpected toxicities.

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**References:**


