Prolonged Progression-Free Survival in a Patient With Triple-Negative Breast Cancer Metastatic to the Liver After Chemotherapy and Local Radiation Therapy

Bryan Chang,1 Joseph Sokhn,2 Edward James,3 Maysa Abu-Khalaf 3

Clinical Practice Points

- Patients with triple-negative metastatic breast cancer (negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) that progresses after standard systemic chemotherapy have limited treatment options and a poor prognosis.

- This report presents the case of a 50-year-old woman with triple-negative breast cancer with liver-only metastases who achieved extended progression-free survival off systemic chemotherapy for approximately 3 years after initial treatment with chemotherapy and precision radiotherapy to her liver metastases.

Keywords: Chemotherapy, Liver metastasis, Radiation, Stereotactic body radiation therapy, Triple negative breast cancer

Introduction

Triple-negative breast cancer (TNBC) is a histopathologic diagnosis based on the absence of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2, ERBB2) (ER−/PR−/HER2−).1 TNBC is associated with a worse prognosis compared with hormone receptor–positive (HR+) tumors. A prospective study by Lin et al2 of 15,204 women between January 2000 and December 2006 found that patients with TNBC had worse breast cancer–specific and overall survival, even after adjusting for various confounding factors. However, TNBC is associated with considerable heterogeneity with respect to clinical outcomes.3

Approximately half of the patients with metastatic breast cancer will develop liver metastases, which are typically associated with a state of widely disseminated disease and involvement of other visceral organs.4 The prognosis of patients with liver or lung metastases is generally inferior to that of patients with bone metastases.5 However, a minority of patients (about 5%) with stage IV breast cancer present with liver-only metastases.5 The prognosis of patients with liver-only metastases may be better than that of patients who have liver metastases and widespread disease.6

This report presents the case of a 50-year-old woman with a diagnosis of TNBC metastatic to the liver who achieved extended progression-free survival after systemic chemotherapy and precision radiotherapy to liver metastases.

Case Report

In August of 2006, a 50-year-old white woman with no medical history or family history of breast cancer palpated a mass in the inferior aspect of her right breast. A mammogram found a 2-cm suspicious mass at the 6-o’clock position, and an ultrasound confirmed the presence of an irregular lobular cystic mass. A fine-needle aspiration was nondiagnostic, and she therefore underwent an excisional biopsy of the right breast in September of 2006, which found a 3.5 × 2.0 × 1.5-cm poorly differentiated infiltrating ductal carcinoma, nuclear grade 3 with necrosis. There was no evidence of lymphovascular invasion. There was also ductal carcinoma in situ, grade III. The invasive tumor was ER−/PR−. There was no HER2 overexpression by immunohistochemistry (score 0), and HER2 gene amplification was not identified by fluorescent in situ hybridization assay; the ratio of HER2 to chromosome 17 centromere (CEP17) was 1.0. The surgical margins were positive at the inked portion of the resected specimen. She underwent genetic testing, which found no evidence of breast cancer 1 or 2 early onset gene (BRCA1 or BRCA2) mutations. Baseline radiographic staging with a computed...
tomography scan of the chest, abdomen, and pelvis (CT C/A/P) in September 2006 found 3 hypodense, enhancing liver lesions consistent in appearance with metastases, ranging in size up to 2.3 cm (Fig. 1). This was confirmed by a subsequent magnetic resonance imaging (MRI) study of the abdomen. A bone scan found no skeletal metastases.

After the diagnosis of metastatic disease, she was started on systemic chemotherapy with weekly paclitaxel at a dose of 80 mg/m² in October 2006, and later bevacizumab at 10 mg/kg was added. While on treatment, she developed a palpable mass at the surgical site in the right breast that grew to a size of 5.6 cm over 2 months (Fig. 2). A biopsy in December of 2006 found a poorly differentiated infiltrating ductal carcinoma, nuclear grade 3, which was similar to her original tumor pathology. The tumor was ER⁻/PR⁻. HER2 status was determined by immunohistochemistry (score 1+), and HER2 gene amplification was not identified by fluorescent in situ hybridization assay (HER2:CEP17 ratio, 1.18). A positron emission tomography—computed tomography scan in December 2006 found increased fluorine-18 fluorodeoxyglucose (FDG) activity in the breast mass (standardized uptake value [SUV], 20.2), the largest liver mass (SUV, 13.0), and FDG activity in a lesion of the right lobe of the liver that had an SUV of 3.9. She enrolled in a clinical trial and was treated with an mTOR inhibitor—containing regimen. After receiving approximately 6 weeks of therapy, she had an increase in the size of the right breast mass. This was confirmed on a CT scan, with the breast mass increasing from 5.6 cm to 8.3 cm in diameter when compared with the pretreatment study. There was also interval increase in the metastatic burden of the liver. Given the concern for the rapid disease progression, doxorubicin at 60 mg/m² and cyclophosphamide at 600 mg/m² were administered, and she received 5 cycles with clinical and radiographic response. Subsequently, in April 2007, treatment was changed to weekly single-agent vinorelbine at 25 mg/m². A follow-up CT C/A/P obtained in December 2007 found resolution of the right breast mass (Fig. 3A) and shrinkage of the hepatic metastases (see Fig. 3B). Vinorelbine was continued until February 2010 for a total of 33 cycles, with good clinical and radiographic response, and she tolerated this regimen quite well. Restaging CT C/A/P in February 2010 found a residual 5-mm left hepatic lobe lesion. A mammogram found benign calcifications with no residual mass in her breast. As a result of the sustained excellent radiographic response of her breast and liver lesions to systemic chemotherapy, the patient was offered a chemotherapy holiday.

The patient then expressed interest in local therapies for the breast and liver. Options including surgery, radiation therapy, and radiofrequency ablation were discussed with the patient, and she elected to pursue radiation therapy. In March 2010, she underwent simulation for the liver lesion, using full-body vacuum bag immobilization with rigid abdominal compression and shallow breathing. A gadoxetate (Eovist)-enhanced treatment-planning MRI scan of the liver was obtained that found only a single 0.5-cm residual tumor nodule, and this was merged with the treatment-planning CT for target definition. Because the tumor was adjacent to the small bowel, a dose of 40 Gy in 10 fractions was chosen to provide a biologically potent treatment while minimizing the risk of toxicity (Fig. 4A, B). The patient tolerated treatment well, with no side effects. She then received a course of 42.5 Gy in 16 fractions to the right breast using standard tangential fields. She developed minimal in-field dermatitis and completed treatment without incident.

She continued to be followed up clinically and radiographically. A CT C/A/P from May 2012 found no evidence of disease. There was a mild hypodensity along the fissure for the ligamentum teres, which was benign. This was in the area of the prior high-dose liver radiation. A mammogram from September 2012 found only postoperative changes in the right breast.

The most recent bone scan and CT C/A/P in May 2013 found no evidence of metastatic disease. Laboratory studies done at the time found normal blood counts, liver function test results, and creatinine levels. Measurements of carcinoma antigens CA 27-29 and CA 15-3 and of carcinoembryonic antigen have been unremarkable.

Discussion

The median overall survival of patients with metastatic breast cancer ranges from 18 to 24 months. The overall survival of patients with metastatic TNBC is reported to be worse when compared with patients with HR⁺ breast cancer. A retrospective study of 3726 breast cancer patients found a median survival of only 6 to 11 months for patients with metastatic triple-negative tumors.
The standard treatment is palliative chemotherapy in most circumstances. A retrospective study of 111 patients with metastatic TNBC found that the median durations of first-, second-, and third-line palliative therapy were 11.9, 9, and 4 weeks, respectively. However, it is important to note that the patient in the present case report had de novo metastatic TNBC. A large retrospective study by Dawood et al involving 3524 women reported that patients with de novo stage IV breast cancer had improved survival compared with patients with relapsed disease. Hellman and Weichselbaum first proposed the state of oligometastatic disease in 1995. They suggested that, in contrast to the traditional concept of metastatic cancer, in which the first few metastases are simply the first visible manifestations of widespread occult cancer, some cancer patients with a limited number of metastases exist in a transitional state between localized and diffusely metastatic disease. Local ablative therapy in such patients might therefore lead to improved control of systemic disease. The European Organisation for Research and Treatment of Cancer (EORTC) compared the first-line therapies of doxorubicin versus paclitaxel through the clinical trial 10923 and of doxorubicin/cyclophosphamide versus doxorubicin/paclitaxel through the clinical trial 10961 in patients with metastatic breast cancer. Patients with liver-only metastases (LOM) comprised 18% of all patients with liver metastases in both the 10923 and 10961 trials. The median survival of patients with liver-only metastases, as opposed to those with liver plus other sites of metastases (LPO), was 22.7 versus 14.2 months in 10923 and 27.1 versus 16.8 months in 10961. These results indicate that the prognosis of patients with liver-confined disease is better than that of those with widespread metastases and that local therapy may be able to affect the course of the disease. However, it is important to note that in both of these trials, the proportion of the various breast cancer phenotypes was not described in detail in the LOM and LPO groups. It is therefore possible that favorable ER+/PR+ phenotypes could represent confounding variables that led to more favorable outcomes in the LOM group.

The rise of new surgical and ablative techniques for liver metastases, combined with data on surgery for liver metastases from colorectal cancer, has sparked interest in local therapy for breast cancer liver metastases. A number of recent series of carefully selected patients have found 5-year survival rates ranging from 10% to 63%. Recently, there has been interest in using less invasive techniques, such as percutaneous radiofrequency ablation and laser-induced interstitial thermotherapy, to treat breast cancer liver metastases. These techniques require percutaneous or intraoperative placement of a probe into the tumor, followed by direct application of high-frequency alternating current or laser energy to heat and ablate the target tumor. Thermal modalities are not indicated for treatment of targets that abut heat-sensitive structures, including the bowel, as in this case. Transarterial chemoembolization or radioembolization are percutaneous techniques that aim to introduce microscopic beads into the part of the hepatic artery feeding the tumor to cause occlusion of the blood supply or to deliver local radiation. These techniques are minimally invasive but are generally reserved for situations with large or multiple tumors. Stereotactic body radiation therapy (SBRT) is a novel, very precise, biologically potent technique for administering external beam radiation in high doses over a small number of fractions. Initial results in metastatic disease have yielded a high degree of local control with

![Figure 3](image1.png)

**Figure 3** Computed Tomography Scans From December 2007. A, Regression of Right Breast Mass After Chemotherapy. B, Regression of Hepatic Metastases

![Figure 4](image2.png)

**Figure 4** Liver Radiotherapy Plan. A, Axial View. B, Sagittal View
few side effects, but the technique is only just beginning to be applied to breast cancer liver metastases. After being evaluated for surgical resection of liver lesions, radiofrequency ablation, and SBRT, the patient opted to have SBRT to treat her residual liver metastases. In this case, the use of a hypofractionated regimen reduced treatment time, and precision immobilization and treatment planning and delivery allowed for safe delivery of high-dose radiation to the liver metastases despite close proximity to the radiosensitive duodenum.

Retrospective analysis of data from single institutions and large randomized studies suggests that TNBC does not have a significantly higher rate of local recurrence after conservative surgery and radiation, although some studies suggest that triple-negative status predisposes women to regional nodal failures. The present patient had initial surgical excision of her breast cancer with positive margins. Multiple studies have found an increased rate of local recurrence after lumpectomy with positive margins, even with adjuvant radiation, and reexcision is typically recommended in this situation. She did not have a reexcision, because she was discovered to have evidence of metastatic disease to her liver. The breast mass grew to greater than 8 cm after the first 2 lines of therapy, which included a taxane combination therapy. Some investigators have proposed that surgical resection of the primary breast tumor improves outcomes in selected patients with favorable presentations of stage IV disease. Although surgical excision was considered for the present patient, given the lack of clinical or radiographic evidence of residual tumor in the breast after her extended course of systemic therapy, radiotherapy to the breast was performed with the intention of eliminating any microscopic residual disease.

Conclusion
The prognosis of women with metastatic breast cancer is variable, and some women with liver-only metastases from breast cancer exhibiting a good response to systemic chemotherapy may benefit from local therapy to the site of metastatic disease, allowing an extended break from chemotherapy administration and related toxicities.

Disclosure
The authors have stated that they have no conflicts of interest.

References
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