

Review of Triple Negative Breast Cancer Cases Treated at Lehigh Valley Health Network in 2013-14

Elliott Goldberg and Savitri Skandan, MD

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the lack of HER2, estrogen and progesterone receptors. Mutation to the BRCA1/2 gene increases susceptibility to several types of cancer, including breast and ovarian, and women with germline BRCA1 or BRCA2 mutations are estimated to have a lifetime risk of 50-85% of developing breast cancer.¹ Frequency of BRCA mutation is observed to be higher in patients with TNBC (~20%) relative to all breast cancer subtypes (~5%).² BRCA mutation is also correlated with a younger age at diagnosis and a higher risk of recurrence.^{3,7} By reviewing TNBC cases seen by Lehigh Valley Health Network (LVHN) in 2013-14, we show that all treatments offered by LVHN are in accordance with the national standard and that 16% of patients tested were positive for BRCA1 mutation.

Introduction

Female breast cancer is estimated to be the most common type of cancer diagnosed in 2015, representing 14% of all new cancer cases in the United States.⁴ Prognoses vary based on the expression of certain receptor proteins by the breast tumor: those expressing receptors to estrogen (ER) or progesterone (PR) can be treated with systemic endocrine chemotherapy in the form of tamoxifen or aromatase inhibitor, which are effective treatments with mild side effects.⁵ Breast cancers can also overexpress receptors to human epidermal growth factor (HER2)—these tumors exhibit rapid growth and sensitivity to treatment with a monoclonal antibody such as trastuzumab, which is also well tolerated.⁶ Breast cancers expressing neither endocrine receptors nor HER2 are called triple-negative and are associated with a poor prognosis due to their resistance to the targeted hormonal or HER2 therapies as well as their apparent aggressiveness relative to other types of breast cancer.⁷ Triple-negative breast cancer (TNBC) has been observed to develop more frequently in pre-menopausal or younger women and displays both higher mitotic grade and larger tumor size at diagnosis.⁷ It is estimated that 15-20% of all breast cancers diagnosed in the United States are triple-negative.³

Susceptibility to TNBC may arise from mutations to the genes BRCA1/2, which encode central proteins to many DNA repair and cell cycle regulatory macromolecular complexes.⁸ At least 13 different tumor suppressor proteins have been found to interact with BRCA1 and BRCA2 and function in homologous-recombination-mediated DNA repair,

apoptosis and cell cycle regulation.⁸ Women with BRCA mutations are estimated to have a lifetime risk of developing breast cancer of 50-85%.¹ BRCA mutations are more common in patients with TNBC (~20%) relative to all breast cancer subtypes (~5%).² In TNBC patients, BRCA mutations have also been correlated with a younger age at diagnosis.^{3,7} It is recommended that all patients diagnosed with TNBC receive genetic screening for BRCA mutation.⁹

Breast cancer was the most common type of cancer treated at Lehigh Valley Health Network (LVHN) in 2013 and 2014. One goal of this study is to determine whether treatments offered to patients with TNBC at LVHN in 2013-14 were in agreement with the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology for Breast Cancer, Version 2.2015. We also determine the frequency of BRCA mutation in the population of TNBC patients seen by LVHN who were referred to genetic counseling and were tested for BRCA mutation. We show that the treatment offered to TNBC patients by LVHN in 2013 and 2014 was in accordance with the NCCN Guidelines and that 16% of patients who received genetic testing were positive for a BRCA mutation.

Methods

All charts of patients who were diagnosed and treated for TNBC at LVHN during 2013 and 2014 were reviewed. 69 total charts were examined: it was found that 5 of these cases were not triple-negative, 1 had no follow-up, and 1 transferred care. The remaining 62 charts were reviewed for information on the patient's age, staging, and treatment, which was determined from all recorded transcriptions including pathology results. Genetic consultations and test results were also reviewed to determine the presence of BRCA mutation. All data analysis was performed using Microsoft Excel. Comparison to the NCCN Practice Guidelines in Oncology for Breast Cancer Version 2.2015 was made to determine whether the treatments offered by LVHN were in accordance with the national standard.

Results

Staging of Triple Negative Breast Cancer Patients at LVHN in 2013-14

Stage	Number of Cases
0	2
1	23
2	21
3	13
4	3

Table 1. Organization of 62 cases of TNBC seen by Lehigh Valley Health Network from 2013-2014 by staging.

Treatments Received for Triple Negative Breast Cancer at LVHN

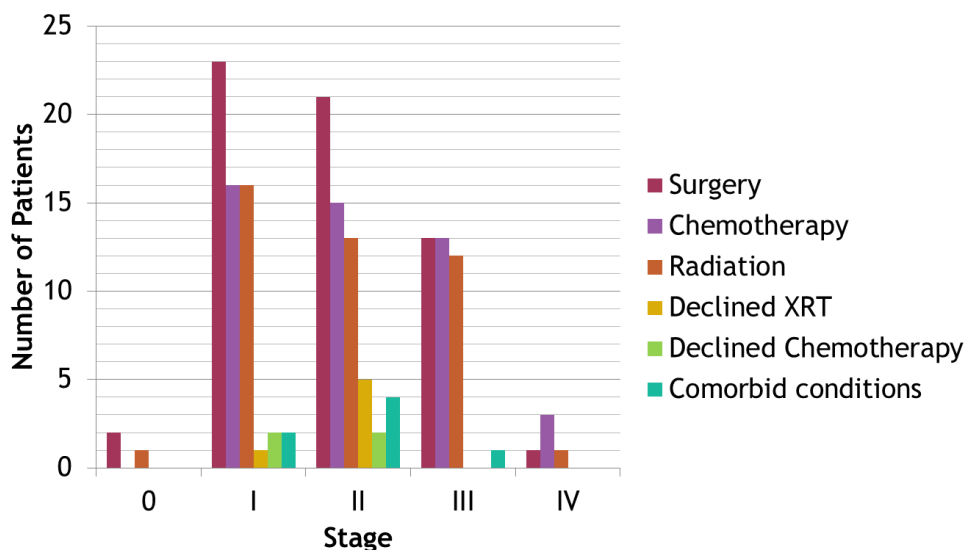


Figure 1. Treatments received by TNBC patients at Lehigh Valley Health Network in 2013-14. Surgery includes either lumpectomy or mastectomy, with surgical axillary staging. Chemotherapy for Stage I patients was given in the adjuvant setting, while chemotherapy for Stage II and III patients was given in either the neoadjuvant or adjuvant setting depending on the tumor size and the timing of the surgery: treatments include combined Adriamycin and Cytoxan followed by Taxol, combined Taxol and Cytoxan, or weekly Taxol. Chemotherapy for Stage IV patients includes the above drugs as well as Doxil, Ixempra, combined carboplatin and gemcitabine, epirubicin, vinorelbine, Xeloda, or 5-fluorouracil given palliatively. Radiation (XRT) includes brachytherapy or beam radiation given in either the adjuvant or palliative setting to the whole breast, axilla, or chest wall. Patients with comorbid conditions were ineligible for chemotherapy and/or radiation.

The first goal of our study is to determine whether treatments offered to TNBC patients at LVHN in 2013-14 were in accordance with the NCCN guidelines. In total, 62 cases of TNBC were reviewed [Table 1]. There were two patients with Stage 0 breast cancers: one was treated with lumpectomy and radiation, and the other was treated with mastectomy [Figure 1]. Both patients had regular follow up visits. These treatments are in accordance with the recommended NCCN guidelines for the treatment of ductal carcinoma in situ which state that either lumpectomy with adjuvant radiation or mastectomy followed by observation and yearly mammograms are appropriate treatments.¹⁰

There were 23 patients who presented with Stage I TNBC [Table 1]. All of these patients were also Stage IA meaning that their tumor was less than 2 cm in its greatest dimension without involvement of the lymph nodes.¹⁰ All 23 of the patients received surgery [Figure 1]. Of these, 16 received breast-conserving surgery, 15 received adjuvant radiation therapy and 1 declined radiation [Figure 1]. The remaining 7 received mastectomies, one of whom went on to receive adjuvant radiation due to her high risk of recurrence [Figure 1]. Of these 23 patients, 16 received adjuvant chemotherapy, 2 were offered chemotherapy but declined, 2 were ineligible for chemotherapy due to their comorbid conditions, and 3 were not recommended chemotherapy due to the size of their

tumor [Figure 1]. All 23 patients attended regular follow up visits. These treatments offered are in accordance with the recommended NCCN guidelines for treatment of localized invasive TNBC which state that either lumpectomy with adjuvant radiation or mastectomy are appropriate treatments, and which recommend chemotherapy in triple-negative tumors greater than 1 cm in greatest dimension or consideration of chemotherapy in triple-negative tumors greater than 0.5 cm with no lymph node involvement.¹⁰ In addition, patients are recommended to attend follow up appointments regularly and receive yearly mammograms.¹⁰

There were 21 patients diagnosed with Stage II TNBC [Table 1]. Of these 21, 14 were Stage IIA, which is defined as any tumor between 2 and 5 cm in greatest dimension without metastasis to lymph nodes or any tumor less than 2 cm in greatest dimension with metastasis to movable ipsilateral axillary lymph nodes.¹⁰ The other 7 patients were diagnosed as Stage IIB, which is defined as any tumor greater than 5 cm in greatest dimension without lymph node metastasis or any tumor between 2 and 5 cm in greatest dimension with metastasis to movable ipsilateral axillary lymph nodes.¹⁰ All 21 of the Stage II patients received surgery: 13 patients received mastectomy and 8 received lumpectomy [Figure 1]. 15 of these patients received chemotherapy, either in the neoadjuvant or adjuvant setting, 2 declined chemotherapeutic treatment, and 3 were ineligible for chemotherapy due to comorbid conditions [Figure 1]. 13 patients received adjuvant radiation therapy, 5 declined radiation, and 2 were not recommended to receive radiation [Figure 1]. One patient had cerebral palsy and was recommended to receive neither chemotherapy nor radiation because she would not tolerate the treatments [Figure 1]. All 21 patients did attend follow up visits. All of the treatments offered by LVHN for Stage II TNBC are in accordance with the recommended NCCN guidelines for treatment of localized invasive TNBC depending on the tumor size: neoadjuvant chemotherapy followed by breast-conserving surgery and adjuvant radiation may be given if the cancer responds sufficiently to the neoadjuvant treatment, with the option of mastectomy if the disease progresses during the neoadjuvant treatment.¹⁰ Total mastectomy without neoadjuvant chemotherapy remains an option as well.¹⁰ Adjuvant radiation is recommended for consideration in mastectomy patients who have axillary lymph node metastases, a tumor greater than 5 cm in greatest dimension, positive surgical margins or negative margins less than 1 mm.¹⁰ In addition, patients are recommended to attend follow up appointments regularly and receive yearly mammograms.¹⁰

There were 13 patients diagnosed with Stage III TNBC [Table 1]. Of these, 6 were Stage IIIA, which is defined as any sized tumor with metastases in ipsilateral axillary lymph nodes that are fixed to one another, or in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases.¹⁰ Tumors metastatic to movable ipsilateral axillary lymph nodes which are larger than 5 cm in greatest dimension are also staged as

IIIA.¹⁰ There was 1 patient with Stage IIIB cancer, defined as an inflammatory tumor or any tumor invasive of the chest wall.¹⁰ There were 6 patients with Stage IIIC cancers, defined as any tumor metastatic to ipsilateral infraclavicular lymph nodes, ipsilateral supraclavicular lymph nodes, or both internal mammary and axillary nodes.¹⁰ Of these 13 Stage III patients, all received surgery: there were 9 mastectomies and 4 lumpectomies [Figure 1]. All of the patients received chemotherapy in either the neoadjuvant or adjuvant setting, or both [Figure 1]. 12 of the 13 patients were offered radiation therapy, and one patient was not recommended to receive radiation therapy due to the extent of her disease [Figure 1]. The patients attended regular follow up appointments. All treatments offered by LVHN for these patients was in accordance with the NCCN guidelines for treatment of Stage III locally advanced breast cancer, which recommends neoadjuvant chemotherapy: if responsive, it recommends lumpectomy or mastectomy followed by radiation to the chest wall and infraclavicular and supraclavicular lymph nodes.¹⁰ If the cancer does not respond to the first line of chemotherapy, additional systemic therapy and preoperative radiation are recommended.¹⁰ In addition, patients are recommended to attend follow up appointments regularly and receive yearly mammograms.¹⁰

There were 3 patients diagnosed with Stage IV TNBC [Table 1]. Stage IV, or metastatic cancer, is characterized by detectable metastases histologically proven larger than 0.2 mm in distant organs.¹⁰ Metastatic breast cancer is not curable, but it can be treated. All three patients received palliative chemotherapy: 2 of the patients received three or more chemotherapy regimens [Figure 1]. One patient received mastectomy, and one patient received palliative radiation therapy [Figure 1]. These treatments are in accordance with the NCCN guidelines for treatment of Stage IV TNBC which recommend three sequential lines of chemotherapy, with or further chemotherapy if the disease responds or transition to palliative care.¹⁰

The second goal of our study is to determine the frequency of BRCA mutations among TNBC patients seen at LVHN in 2013-14. All 62 patients were eligible to receive genetic testing as a result of their triple-negative diagnosis: of these 62 referrals, 25 followed up with the genetic counselor and underwent genetic testing.⁹ 4 patients tested positive for a mutation to the BRCA1 gene. None of the patients in our study tested positive for a BRCA2 mutation. These results indicate that 16% of TNBC patients seen by LVHN in 2013-14 who received genetic testing carried a mutant BRCA gene. This result is consistent with the literature findings which suggest 15-20% of patients diagnosed with TNBC have a mutation in BRCA1.² Furthermore, the average age of TNBC patients diagnosed at LVHN in 2013-14 was determined as 61 years, while the average age at diagnosis for TNBC patients with BRCA mutation was significantly younger at 47 years. This result is also consistent with the literature suggesting that BRCA mutation is correlated with a younger age at TNBC diagnosis.³

Conclusions

The goals of our study were to determine if the treatments offered to TNBC patients treated at LVHN in 2013-14 were in accordance with the NCCN Guidelines Version 2.2015 and to determine the frequency of BRCA mutation among the population of those patients who had received genetic testing. We have shown the treatments offered to TNBC patients in 2013-14 were in accordance with the national guidelines. We have also determined the incidence of BRCA1 mutation to be 16% in a population of 25 TNBC patients who received genetic testing. Our results show the average age of BRCA mutant TNBC patients (47) to be significantly younger than the average age of all TNBC patients in our study (61). However, we report that of the 62 patients in our study, only 25 received genetic testing (~40%). A further subject of interest may be methods to mainstream these genetic tests. We hope that BRCA screening will gain more popularity in the future as a prognostic factor.

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