

Teaching Case

Triple Negative Breast Cancer in a Male to Female Transgender Patient: A Case Report and Literature Review



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Introduction

In recent years, there have been a growing number of transgender patients seeking medical care in the United States.¹ Current estimates suggest that approximately 1 million Americans identify as transgender, with these numbers continuing to grow.^{2,3} Transgender people have historically had a wide array of discriminatory practices leading to poor mental health, suboptimal medical care, and worse health care outcomes.⁴ Recently, a greater emphasis has been placed on helping to support this cohort of patients with hormonal medications and surgical affirmation, which has led to an improvement in emotional well-being.⁵ Despite advances in the treatment of transgender patients, there remain unique challenges in establishing the optimal treatment paradigms for these patients. From an oncologic perspective, where the use of screening and hormonal manipulation can be of high importance, there remains little guidance in how to best care for transgender patients. Additionally, many physicians also may struggle with the complex psychosocial issues encountered when taking care of this population.

We present a case study of a transgender female patient who developed triple negative (TN) carcinoma of the left breast and was treated with neoadjuvant chemotherapy followed by lumpectomy with sentinel lymph node biopsy and adjuvant radiation treatment. We also present a review of the relevant literature.

Case Presentation

Our patient is a black transgender woman who first self-identified as female at age 5. She began pursuing gender affirming physical changes by undergoing orchiectomy at the age of 19. She subsequently initiated long-term exogenous estrogen therapy, which was continued for 33 years. She also underwent silicone facial injections in her 20s to achieve a more feminine appearance. At the time of her breast cancer diagnosis, she was receiving injections of 10 mg of estradiol valerate every 14 days. With this use of hormone therapy, the patient experienced mammary development and achieved a breast volume within the normal range for an adult cisgender woman. She endorsed no family history of breast cancer and screening mammography was initiated at age 43, with no evidence of malignancy. Her most recent mammogram, less than 1 year before the breast cancer diagnosis, showed stable bilateral calcifications, BI-RADS category 2.

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At age 53, the patient noted a left axillary mass and presented for medical evaluation. Computed tomography (CT) scan of the chest revealed that the mass correlated with a 2.9-cm axillary node; also noted were enlarged subpectoral nodes and skin thickening of the left breast. Surgical excision of the axillary lymph node was performed at an outside hospital revealing poorly differentiated metastatic adenocarcinoma with immunohistochemical stains suggestive of a primary lung cancer. At that time, she was referred to our institution. The lack of lung findings on imaging and the detection of left breast skin thickening on the original CT suggested that the cancer might be of breast origin. Clinical examination performed by the evaluating breast surgeon revealed nonerythematous skin thickening and peau d'orange confined to the inferior central left breast, adjacent to the nipple-areolar complex. A palpable mass was noted in the upper inner quadrant and postoperative change was noted in the axilla. No supraclavicular or cervical adenopathy was appreciated. Breast imaging revealed a 1.9 cm mass in the 10:00 axis with adjacent satellite lesions, as well as axillary adenopathy (Fig. 1). Core biopsy of the left-breast 10:00 lesion revealed invasive carcinoma, poorly differentiated, with anaplastic features, associated with a prominent lymphocytic background. Extensive lymphovascular invasion was present. The carcinoma was morphologically consistent with breast origin and was morphologically similar to the material obtained from the left axillary biopsy. The tumor was negative for estrogen receptor, progesterone receptor, Her2, androgen receptor, mammaglobin, BREAST-2, globin transcription factor-3, paired box gene 8, and thyroid transcription factor 1. Positron emission tomography CT demonstrated a left subpectoral node, measuring 2.5×3.3 cm (standardized uptake value max 17.4), as well as a focus of uptake in the medial left breast, without a definite CT correlate but an standardized uptake value max 7.8. No evidence of metastatic disease was identified. The patient was clinically staged as IIA (T1cN1M0) according to the American Joint Committee on Cancer eighth edition. Genetic testing with Myriad MyRisk panel (including *BRCA 1-2*, *ATM*, *PALB2*, *PTEN*, *CHEK2*, and *TP53*) showed no clinically significant mutations. Significant comorbidities included human immunodeficiency virus, which was well managed on highly active antiretroviral therapy, with a non-detectable viral load, and a history of dysphoric feelings manifested as anxiety and depression, managed by a psychiatrist without the use of medication.

Although her tumor did not express hormonal receptors, there was concern that, owing to the known plasticity of breast cancer stem cells and the high degree of intratumoral heterogeneity seen in breast cancer, additional estrogen therapy may encourage the development of an estrogen receptor–positive subset of her tumor or even lead to the development of a second primary tumor. A multidisciplinary decision was therefore made to

discontinue estrogen therapy at that time, with the understanding that this discussion could be revisited if the adverse effects of stopping estrogen therapy began to outweigh the potential benefits. Neoadjuvant chemotherapy was initiated and she received 4 cycles of dose dense doxorubicin and cyclophosphamide followed by 12 cycles of paclitaxel and carboplatin. During treatment, periodic physical examination noted resolution of the palpable breast mass and a significant diminution of axillary disease. Chemotherapy was largely well tolerated, with mild nausea, managed effectively with antiemetics. Physical examination after completion of chemotherapy noted complete resolution of skin changes with decrease in size of the palpable left axillary node. Posttreatment magnetic resonance imaging showed no residual enhancement in the left breast and positron emission tomography scan showed a favorable response to therapy, with resolution of the (18)F-fluorodeoxyglucose avidity in the left breast and axilla.

One month after completing chemotherapy, the patient underwent lumpectomy and sentinel lymph node biopsy. Pathology review demonstrated no residual carcinoma identified within a fibrotic tumor (measuring 35 mm). Scattered foci of ductal carcinoma in situ (high-grade), located within 1 mm of the inked medial margin were noted. No lymphatic invasion was identified. Four sentinel nodes were retrieved, one of which was partially fibrotic but negative for carcinoma and one contained up to 25 isolated tumor cells in the subcapsule. Re-excision of the medial margin was not pursued as the lumpectomy had extended to the sternum.

Our patient was subsequently treated with a course of adjuvant external beam radiation therapy to the left breast and regional lymph nodes (axillary, supraclavicular, and internal mammary nodes) to a dose of 50.4 Gy in 28 fractions. Treatment was delivered using 3-dimensional (3D) conformal radiation treatment (3D CRT). Planning was done with field in field technique using mixed 6 MV and 16 MV photons. This was followed by a boost to the lumpectomy cavity using 3D CRT with 6 MV photons for an additional 14 Gy in 7 fractions owing to the close ductal carcinoma in situ margins. The patient tolerated radiation treatment well, with expected skin changes, including diffuse hyperpigmentation (RTOG grade 1-2), which was managed effectively with topical emollients. She did not develop overt desquamation.

Since completing treatment, the patient has been seen in regular follow-up visits by her treating physicians. Subsequent imaging studies of the breast and axilla have revealed no worrisome findings. On 2 occasions, nodularity was appreciated on physical examination; first in the left axilla, and then in the left breast upper outer quadrant by the surgeon. Fine-needle aspirations were performed, revealing fat necrosis. At her most recent follow-up visit, which took place 18 months after completing radiation treatment, the patient continued to

recover well. A mammogram obtained prior to this visit showed no evidence of recurrence (Fig. 2). Physical examination also showed no evidence of disease. Mild hyperpigmentation of the treated breast was apparent. The left breast was mildly edematous, slightly firmer to palpation, and mildly retracted superiorly compared with the contralateral nonradiated breast. The patient is disappointed with the cosmetic appearance of the radiated breast due to the asymmetry and is considering plastic surgery evaluation to correct the asymmetry. She is feeling well physically since discontinuing estrogen therapy, although she has noted increased fatigue. She did experience worsening of her anxiety and depression after estrogen cessation due concerns over her gender identity, for which she follows closely with a psychiatrist. Since completing her oncologic care, she has also pursued further facial feminization procedures. At this juncture, she is seen in regular follow up visits by her multidisciplinary team.

Discussion and Literature Review

Transgender patients are seeking medical care at increasing rates in recent years.¹ Although physicians are continuing to evolve their practices to meet the needs of these patients, there remains a dearth of information on how to best manage this population in regards to oncologic care. This patient's presentation raises a number of important issues.

Definitions of Common Terms Related to Gender Identity and Expression

According to the Center of Excellence for Transgender Health at University of California, San Francisco, gender identity can be defined as “a person's internal sense of self and how they fit into the world, from the perspective of gender,” whereas gender expression is a person's outward expression of their gender. They also define transgender as “a person whose gender identity differs from their assigned sex at birth.”⁶ Therefore, a person assigned male sex at birth but identifies as a female can be described as a transgender female and a person who was assigned female sex at birth but identifies as a male can be described as a transgender male.

What Are the Effects of Hormonal Therapy on the Development of Breast Cancer?

Hormonal therapy is an integral component of treatment for transgender female patients and is an intervention that is typically continued indefinitely unless contraindications arise.⁷ In our patient, estrogen therapy led to the development of a significant amount of breast

tissue but in most cases, estrogen therapy appears to have a minimal effect on the development of breast tissue, as only 10.7% of patients on estrogen therapy develop an “A” cup or larger bra size at 1 year.⁸ It is unclear why our patient developed significantly more breast tissue than the average transgender patient. Research has shown that in addition to altering physical appearance, hormonal therapy improves psychologic outcomes and quality of life in transgender patients and thus plays a critical role even in patients who do not experience significant cosmetic changes.⁹ Therefore, balancing cancer treatment and hormonal treatment is of the utmost importance in these patients, as psychologic, physiologic, and oncologic outcomes all need to be carefully considered.

As the majority of male breast cancers are estrogen and progesterone receptor positive (75% luminal A, 21% luminal B, and 4% basal-like or TN), it can be difficult to differentiate between male breast cancers and those possibly driven by estrogen administration, although there are significant differences in other molecular markers.^{9,10} This is of particular interest in our case, as our patient developed a TN breast cancer that does not appear to be driven by hormonal therapy. Additionally, although estrogen exposure is a known risk factor for the development of breast cancer in cisgender females, there is conflicting data as to whether the use of exogenous estrogens in the transgender female population actually increases the risk of breast cancer. A number of small series have shown no significant increase in breast cancer incidence in the transgender female population compared with cisgender males, although a recent study by de Blok et al showed a 46-fold increase in incidence in patients receiving hormonal therapy compared with cisgender males.¹¹⁻¹⁴ Therefore, it remains unclear as to whether or not the psychosocial and cosmetic benefits of hormonal therapy outweigh the potential risk of developing breast cancer and how best to discuss these issues with patients.

Gaps in the Hormone Therapy Literature

The use of adjuvant antiestrogen therapy in transgender female breast cancer patients is not fully understood and may result in an increased burden to patients. Although in cisgender women there is clear evidence to support the use of tamoxifen or aromatase inhibitors in estrogen receptor positive cancers, the data are less clear in male breast cancer and even more limited in transgender female patients. Although tamoxifen has been shown to be effective in reducing distant metastases and improving survival in male patients with positive hormonal receptor status, the role of aromatase inhibition or androgen suppression is not fully understood and remains under investigation with the ongoing A prospective, randomised, multi-centre phase II trial to evaluate oestradiol suppression in the case of (neo)adjuvant and palliative

treatment with tamoxifen alone versus tamoxifen plus GnRH analogue versus aromatase inhibitor plus GnRH analogue for male breast cancer patients—German Breast Group (MALE-GBG54) trial.^{15,16} Therefore, in transgender female patients on hormonal therapy diagnosed with hormone-receptor positive tumors, whose breast cancer may be biologically different than both cisgender males and females, it is unclear which antiestrogen therapies would be most beneficial, with tamoxifen being the treatment of choice at this time.

How and When Should Breast Cancer Screening Be Done?

Data remains limited on how to appropriately perform screening on transgender females. Current recommendations are based on screening guidelines for cisgender women, while considering the differences in these 2 populations.

According to a recent review, transgender female who received a diagnosis of breast cancer tended to be diagnosed at a younger median age (51.5 years) compared with both cisgender female (60 years) and cisgender male (68 years) patients.¹⁷ This suggests that transgender female patients may benefit from screening beginning at a younger age than their cisgender female counterparts, which is typically recommended starting at age 50.¹⁸ However, according to 2 cohort studies in transgender women, the incidence of breast cancer in this population remains low, between 4.1 and 20 per 100,000 patient years, compared with cisgender females, in whom the incidence is as high as 170 cases per 100,000 patient years.^{11,19} In addition, the review by Hartley et al, which included transgender female patients, demonstrated that only 13.6% of patients who received a diagnosis based upon screening mammography.¹⁷ Albeit a small sample size, this rate is significantly less than the 43% rate seen in cisgender women.²⁰ Thus, although the “Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People” from University of California, San Francisco generally recommends beginning at age 50, the aforementioned information and the lack of randomized evidence illustrates that it is not entirely clear when initiating screening mammography is most appropriate.⁶ Therefore, an informed discussion surrounding the risks and benefits of screening before the age of 50 followed by a shared decision making process may be a reasonable approach to addressing the question of when to begin screening.

Mammography is typically used as the primary screening modality in both cisgender and transgender female patients. A recent cohort study of 50 transgender female patients who underwent screening mammography, 94% of whom were on estrogen therapy, reported that while mammography was well tolerated and adequate

imaging was obtained, 60% of patients were found to have dense or very dense breasts.²¹ This finding of increased breast density has previously been noted in cisgender women receiving exogenous estrogen replacement therapy and has been associated with an increased risk of false positive and negative findings, in addition to being an independent risk factor for breast cancer.²² It is important to note that the vast majority of the transgender patients in the aforementioned study had also undergone prior breast augmentation, consistent with other series showing that up to 60% to 70% of transgender woman seek breast augmentation in addition to hormone therapy.⁸ The addition of ultrasound in patients with dense breasts can increase the detection of cancers and, therefore, may be considered in most transgender women undergoing screening.²³ Other screening modalities, such as diagnostic breast tomosynthesis and breast magnetic resonance imaging, should also be considered in select high-risk patients, as these imaging techniques can increase rates of cancer detection in patients with dense breasts, while recognizing the risk of increasing false positive results.²⁴ Therefore, it seems appropriate to discuss the use of routine screening with mammography and ultrasound while addressing the risks and benefits of using additional methods of screening.^{21,25}

Specific Challenges in Radiation Oncology

Caring for transgender women with breast cancer poses unique and significant challenges to radiation oncologists. These include consideration of both physical and psychosocial issues. Specific areas of consideration include:

The physician–patient relationship

Formal education for radiation oncologists in the management of transgender patients should be considered, as data has shown limited exposure and understanding of pertinent issues by physicians.^{26,27} One way to achieve this may be to incorporate education on transgender patients into radiation oncology residency education. Honing the skills to form a physician-patient relationship based on trust and respect, while important in all patient care, may have an even greater effect in caring for this unique patient population. The treating physician needs to be able to gain the trust of transgender patients to allow for sharing of sensitive information to allow for optimal care.

Treatment planning considerations

Special technical considerations should be made when treating transgender females with breast cancer. For example, owing to high levels of testosterone during

development and subsequent exogenous estrogen exposure, transgender female patients may have unique anatomy of the chest compared with cisgender males and females, with data showing differences in nipple location and body habitus.²⁸ Therefore, careful attention should be paid to delineating the appropriate target volumes to ensure adequate coverage of high-risk areas. Additionally, high rates of prior breast augmentation can lead to an increased risk of complications in cases treated with breast conserving surgery and radiation to the preexisting implant, such as capsular contracture and poor cosmetic outcomes, although the data are mixed and limited.^{29,30} Additionally, transgender patients likely experience similar risks of reconstructive failure and high-grade capsular contracture as their cisgender female counterparts in the setting of postmastectomy radiation applied to tissue expanders or permanent implants.³¹ These considerations may be even more critical in transgender females, many of whom achieve a great deal of satisfaction after gender-affirming breast surgery.³² Additional data in the transgender population supports improvement in breast satisfaction, sexual well-being, and psychologic health after undergoing breast augmentation when using the widely validated Breast-Q scoring system.^{32,33} Thus, special attention should be paid to optimizing cosmetic outcomes by focusing on details such as reducing dose inhomogeneity (minimizing the maximum dose and the volume of breast tissue receiving >105% of the dose), which can be affected by the presence of an implant and possibly even by the increased breast tissue density seen in transgender female patients.^{21,34,35}

Although cisgender women appear to be largely satisfied with their choice of surgical management of their breast cancer, data are lacking for transgender female patients.^{36,37} Therefore, an early, multidisciplinary discussion with representatives from plastic and oncologic surgery, radiation oncology, medical oncology and other members of the care team about both oncologic and cosmetic outcomes of different surgical and radiation therapy approaches is important and would likely result in improved outcomes and patient satisfaction.

Clinical practice considerations

Specific psychosocial factors pertinent to this patient population need to be considered in the radiation oncology clinic. Many transgender patients have a history of difficulty accessing providers with experience treating patients like them and may have faced discrimination within the health care system.^{27,38,39} Formal education for clinical and nonclinical staff regarding issues involving the transgender community is an important factor for providing optimal care. For example, daily clinical routines should be respectful, including not assuming a patient's gender identity, using appropriate pronouns, and

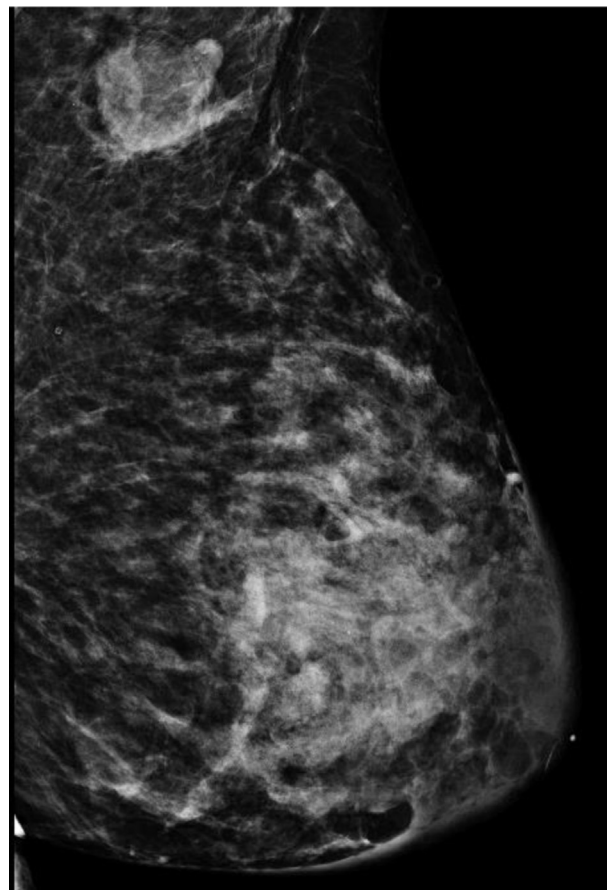


Figure 1 Mediolateral oblique mammogram of left breast before treatment (BI-RADS-V).

providing educational materials that are inclusive of transgender patients. Specific to radiation oncology, the presence of gender binary changing rooms have the potential to make transgender patients uncomfortable presenting for daily treatments.^{26,27} Efforts should be made to allow patients to choose facilities that most closely align with their gender identity or the use of a gender-neutral facility should be offered, per guidelines published by Deutsch et al.⁶ It is the duty of the radiation oncology community to engage in a dialogue with our transgender patients, leaders in local LGBTQ communities, and hospital staff to identify the unique needs of transgender patients, take steps toward meeting these goals and develop comprehensive guidelines for optimizing care. Finally, it is important that we report on the experiences of transgender patients in the literature to help improve our understanding of the complex issues surrounding this population and move toward shrinking health care disparities.²⁶

Conclusions

We presented a case of a transgender female patient who presented with locally advanced TN carcinoma of the



Figure 2 Mediolateral oblique mammogram of left breast at last follow-up (BI-RADS-II).

left breast who achieved a significant response to neoadjuvant chemotherapy followed by breast conservation therapy. This case brings to light many questions regarding the most appropriate way to manage transgender female patients in both the screening for and treatment of breast cancer. Many questions remain unanswered. Although it seems logical to treat these cases with a similar paradigm as for cisgender patients, there are significant socioeconomic, psychologic, biologic, and logistic differences that present unique challenges to radiation oncologists. A strong emphasis should be placed on improving shared decision making between the patient and provider to establish trust and identify the issues most important to the patient. Additionally, efforts should be made at a health care system level to reduce barriers to care and promote inclusion of a patient population that has been historically underserved. Finally, it is important that we report on the experiences of transgender patients in the literature to help improve our understanding of the complex issues surrounding this population and improve outcomes.²⁶

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