



When Breast Cancer Hits, Women Hit Stronger

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Abstract

Breast cancer is the leading cause of cancer related mortality in women. With the advances in treatment and the wide prominence of screening, it has also become the most prevalent cancer. Treatment has mainly been guided by the stage of the disease and the receptors that are expressed by it. Treatment approaches include systemic chemotherapy, surgery with axillary lymph node dissection, radiation therapy, and targeted therapy however not without the cost of physical and psychological drawbacks.

Besides the gastrointestinal side effects and the alopecia related to cancer drugs, women undergoing chemotherapy experience chronic somatic, mood and cognitive changes. Breast surgeries, with or without reconstruction and axillary lymph node dissection, create an irreversible scar not only on the woman's body but also on her psyche. Hormonal imbalances due to chemo or endocrine therapy further exacerbates debilitating physical menopausal-like side effects, fertility troubles and sexual dysfunction. Adding all those psychological and emotional stressors to the physical side effects of treatment has detrimental effects on the woman's femininity and her perception of her own body. Improvement in breast cancer treatment increased the survival rate, but it was at the expense of the psychological status of the women and their quality of life.

Keywords: Breast Cancer; Psychosocial; Treatment Side Effects; Mental Health; Quality of Life

Introduction

In 2020, 2.3 million women were diagnosed with breast cancer proclaiming it the highest incidence of cancer in women. In the same year, 685,000 deaths were recognized globally as breast cancer related, making it the leading cause of cancer related mortality [1]. Additionally, breast cancer was marked as the world's

most prevalent cancer by the end of 2020 affecting 7.8 million women alive who were diagnosed within the past five years [2]. Improvement in survival did not begin until the early 1980's with the introduction of screening for early detection and advances in the different treatment modalities [1]. According to the World Health Organization (WHO), countries have succeeded in reducing

annual breast cancer mortality by 2-4% per year, a success attributed to advances in treatment modalities, however not without a price. The side effects of different cancer treatments impact these women's daily life physically and psychosocially. Consequently, understanding and treating the side effects of breast cancer therapy becomes fundamental.

Breast cancer types

Breast cancer (BC) is classified based on the origin of the tumor cells and the extent of the invasion of surrounding fatty and connective tissues. In fact, BC originates either from the cells lining the ducts (ductal cancers) or cells lining the lobules (lobular cancers). It is divided into non-invasive or carcinoma in situ, and invasive or infiltrating carcinoma. Invasive BC is further classified as either locally advanced or metastatic. Additionally, BC is categorized as hormone positive [when expressing estrogen receptors (ER) or progesterone receptors (PR)], human epidermal growth factor receptor 2 (HER2) positive, triple negative when none of these receptors is expressed. These classifications guide the choice of treatment modalities [2].

Overview of treatment of breast cancer

Surgery

Surgery is part of the multidisciplinary approach in breast cancer management be it in the early or advanced stages of breast cancer. The main goal of surgical resection is to improve survival, achieve local tumor control and prevent regional recurrence [3]. Over the past 30 years, new surgical approaches have developed, aimed at preserving the breast integrity after tumor resection with the recent introduction of "oncoplastic techniques". Total mastectomy with immediate reconstruction remains an alternative in select cases of locally advanced breast cancer.

Breast conserving therapy (BCT) and oncoplastic approaches

BCT remains the preferred surgical option in patients with early breast cancer, those with tumor size of less than or equal to 2 cm, and with locally advanced tumors after neoadjuvant approaches in certain tumor subtypes such as triple-negative and HER-2 positive phenotypes. With BCT, careful histologic assessment of resected margins is necessary with efforts made to ensure negative margins during initial surgery [4]. Negative margins have no tumor cells on ink section and are labeled "no tumor on ink" [5]. This is vital to achieve during the initial surgery because of the increased risk

of regional recurrence with positive margins, leading patients to require a second surgery consequently delaying adjuvant therapy initiation, a delay that comes with an increased physical and psychological stress [3].

To decrease margin positive resections and redo surgeries, oncoplastic techniques were introduced. This approach combines oncologic and plastic surgery thus maintaining a balance between resection of large amount of breast tissue with margins less frequently involved and cosmetic outcomes [3]. Oncoplastic approach enhances quality of life by taking into consideration scar positioning with a suitable reconstruction technique without compromising oncologic safety [6].

Mastectomy

Mastectomy followed by reconstructive surgery is still the preferred approach in selected cases: multicentric disease, large tumor size, patient preference, contraindications for radiotherapy, and inability to attain clear margins with conservative techniques [4]. Various techniques are available and modified when mastectomy is the approach of choice:

- Modified radical mastectomy indicated when tumor involves the skin
- Skin sparing mastectomy removes all glandular tissue preserving the natural skin
- Nipple sparing mastectomy removes breast tissue while preserving nipple-areola complex [4].

Finally, axillary lymph node dissection (ALND) is vital during any surgical approach. Regional lymph node status plays a vital role in treatment selection and prognostic outcome in breast cancer [5]. However, ALND is associated with lymphedema, and may result in nerve injury in some cases [4]. Therefore, sentinel lymph node (SLN) biopsy which is a minimally invasive method was developed and is now the standard of care in patients with low probability of axillary involvement. If the SLN shows evidence of metastatic disease only then would a complete ALND be done. It is important to note that even with SLN, we still do not have a unified algorithm for the extent of ALND which unfortunately in some cases is leading to either under or over surgical treatment of the axillary area. Some identified factors that can direct the extent of ALND include SLN

aspect, S classification for depth of tumor invasion, differentiation between micro and macrometastasis, and microanatomic location of tumor deposit in SLN [7].

Radiation therapy

Postoperative radiation therapy remains the mainstay of care for patients after breast conserving surgery and mastectomy with lymphatic drainage radiation. Adjuvant radiation therapy decreases local recurrence, increases regional control of disease in patients with locally advanced cancer and plays a part in palliative approaches in metastatic disease [8].

As with advances in oncologic surgical approaches, radiation therapy has evolved over the past decade whereby today we can individualize each patient's treatment with the added benefit of minimizing early- and late-term toxicity [9]. Early side effects include erythema and burns of skin in targeted areas with desquamation, they occur two to three weeks into radiation therapy, and they are temporary. Late complications such as heart failure, pulmonary fibrosis, and brachial plexus injury are irreversible and begin to manifest three to six months after initiating radiation therapy [8].

As mentioned earlier, radiation therapy is also a part of multimodal approach in palliative treatment of metastatic disease. The purpose of palliative radiation therapy is to minimize pain due to bone metastasis and minimize neurologic deficits of spinal cord compression caused by tumor deposits [8].

Systemic treatment

Systemic treatment remains a cornerstone in the treatment of breast cancer. It comprises chemotherapy, endocrine, targeted therapy and immunotherapy. The choice of systemic treatment is based on the type and stage of breast cancer as well as multiple prognostic factors including the age of the patient. The benefits of systemic therapy were shown in preventing recurrence of breast cancer and metastases in DCIS [10] and early-stage invasive breast cancer, achieving pathological complete response with neo-adjuvant chemotherapy prior to surgery associated with improved survival and controlling disease progression and metastases in advanced stages [11].

Triple negative breast cancer, as its name indicates is not sensitive to endocrine therapy but is greatly responsive to chemothera-

py. The backbone of chemotherapy regimens in breast cancer comprises anthracycline-based regimens and taxane-based regimens.

Hormone-Receptor positive breast cancer can be treated with both chemotherapy and endocrine therapy. Chemotherapy is warranted based on multiple factors that include disease burden, histologic factors, and genetic studies. If no chemotherapy is deemed necessary or after the completion of chemotherapy, the endocrine therapy plays a major role in preventing disease recurrence and reducing the mortality risk. The backbones of endocrine therapy are Tamoxifen and Aromatase Inhibitors (AI) with or without ovarian function suppression (OFS), with superiority of AI in postmenopausal women [12]. However, endocrine therapy is not only limited to AI or tamoxifen, it also includes in the advanced setting the cyclin-dependent kinase 4/6 Inhibitors (CDK4/6i), mammalian target of rapamycin inhibitors (mTOR i), selective estrogen receptor degrader (SERD) and phosphoinositide 3-kinase inhibitors (PI3K inh) [13].

Treatment of breast cancer also witnessed a breakthrough with the understanding of the HER-2 positive condition. HER-2 targeted therapies, such as monoclonal antibodies (Trastuzumab and Pertuzumab), and tyrosine kinase inhibitor (Neratinib), improve disease free survival (DFS) and reduce breast cancer-related mortality when added to chemotherapy [14,15].

Immunotherapy can also be an option for breast cancer treatment when the tumor expresses a positive PDL-1. Immunotherapy was proven effective when added to chemotherapy with the benefit showing in metastatic cases and unresectable triple negative tumors mainly.

Breast cancer psychology

Women with breast cancer undergoing chemotherapy experience many adverse fallouts on physical, psychological, and social functioning [16]. Early or late stressful side effects change their quality of life and trigger adaptive responses [16,17]. It is noted that patients' concerns about the side effects accompanying chemotherapy change over the course of treatment. At the time of diagnosis, women waver to near term toxicities from chemotherapy for any percent survival gain. However, with time, survivors begin focusing on living beyond the chronic and incapacitating mental effects from adjuvant chemotherapy [17]. Ultimately, quality of life and psychological wellbeing has become a priority.

Physical changes

Once faced with the diagnosis of BC and chemotherapy plan, women primarily fear the most known side effects of chemotherapy-nausea, vomiting, hair loss and fatigue. However, the experience is personalized, and differences may be attributed to the chemotherapy regimens, the cancer stage and patient's age [16]. Fortunately, with advances in pharmacology and better understanding of pathophysiology of nausea, newer generation of antiemetic drugs has helped in managing the gastrointestinal symptoms.

Even though not permanent, alopecia remains an unresolved body image concern reported over years by patients [18]. Hair is looked at as a sign of femininity, consequently hair loss significantly affects the women's image of themselves contributing to social isolation and the inability to enjoy an active life [19]. So far, there are still no pharmacologic interventions proven to decrease hair loss though promising results are seen with the scalp hypothermia.

Fatigue was the most persistent and debilitating symptom attributed to the cancer itself and its treatment, tenacious even in survivors with no evidence of active disease [20]. The underlying pathophysiology is not completely understood, however it can be related to anemia, insomnia, nutritional deficiencies and metabolic disturbances [19]. Fatigue was expressed as constant lethargy and weakness not alleviated by resting or sleeping [16]. It was also described as the inability to perform the daily life activities. Fatigue is completely shattering and debilitating to women and is regarded as the most powerful negative influence on the quality of life [20,21]. One patient even described: "I have so little energy to do stuff and then I lie down and I can't imagine ever moving again. I literally don't move a muscle. It's a different kind of fatigue than just being tired" [22].

Mood and cognitive changes

During the chemotherapy journey, women are overwhelmed with worry, fear, sadness, anxiety, depression, and uncertainty. They worry about the loss of independence and becoming the care receiver instead of caregiver [19]. Women cannot maintain functions as a wife, a mother or a daughter [16]. "I feel I'm not giving enough of myself to my family and especially my baby. I want to do things for my family and right now I can't. It's sad; I can't even wash my baby's clothes or iron them. I am dependent on my mother, and I hate being dependent on other people" stated one mother with

breast cancer [22]. Women fear the separation from their families, the probability they will not be cured, the uncertainty of cancer recurrence and eventually death. They also lose interest in life up to the point of having suicidal ideations [16]. In fact, cancer related depression parallels cancer related fatigue. Breast cancer patients with moderate to severe depression requiring treatment increased from 4.0% before chemotherapy to 30.0% after completing chemotherapy [21]. Cancer related depression is often overlooked and underrecognized and if not properly addressed is associated with increased all-cause mortality [23].

Women with breast cancer reported cognitive problems after chemotherapy completion with memory impairment being their greatest concern, a phenomenon known as chemo brain. It was associated with decline in day-to-day functioning and work ability [24,25]. Short term memory issues were related to the inability to recall what they were doing while in process of doing it, while long term memory was related to the inability to recall important events or scheduled appointments [25]. Certainly, this impairment exacerbated the symptoms of anxiety and depression [24]. In addition, women reported reading comprehension, speed of processing and word finding were affected [25]; "I would lose interest. I would lose where I was at in the book. I would lose the line. I would read a paragraph three times and it still wasn't sinking in" [22].

Psychological impact post-surgery

Cancer patients undergo surgeries all the time- colectomies, pancreatectomies, hysterectomies but all these organs removed are internal organs, nothing seen by the naked eye except for the breast. After surgery, women not only have to physically recover but also must prepare themselves to personally face this new body of theirs on one hand and society on the other, a process which is often mentally consuming and exhausting for cancer patients [26]. This physical loss produces behavioral, emotional even cognitive changes in women after surgery directly influencing their self-esteem [27]. Thus the therapeutic response after mastectomy does not only depend on the physiologic condition of the breast post op, but also on the woman's health as a whole [28]. Hence, preserving mental health is as pivotal as preserving physical health.

Barcia stated, "mastectomy causes more trauma than the cancer illness itself" [26]. As discussed earlier, BCS and mastectomies play a vital role not only in treatment of breast cancer but more

importantly in survival benefit as an outcome. Chemotherapy and radiation therapy treatment side effects may be temporary, managed medically and subside after treatment completion in contrary to surgical removal of a body organ whereby side effects can last a lifetime. To preserve the natural appearance of the breast, immediate breast reconstruction during mastectomy procedures has become a widespread standard over the years in select patients. It has been noted that women who undergo mastectomy without breast reconstruction exhibit more distress from their appearance and body image compared with women who undergo reconstruction [29]. In addition, women who underwent BCS reported more satisfaction with their body image compared to women who underwent mastectomy with and without reconstruction. This is to say that whatever the surgery is the outcome is still the same, dissatisfaction. Dissatisfaction not with the breast removal and potential cancer cure per se but with the aftermath of what remains after the surgery, described as mutilation by some.

Although we are still preserving the breast appearance with reconstruction, scarring remains a major source of distress and is a post-operative concern in most women. Scar appearance in color, irregularities, and thickness can be a source of dissatisfaction in addition to itching and pain which can be experienced at the surgery sight [30]. Daily physical limitations were reported in women in one study whereby more than half of the women mentioned that the scar affected their arm movements subsequently impacting their work, sleep, and housekeeping. The constant awareness of a scar being present is also an area of distress which hinders social functioning like sports or going out in public or even discussing the scars to others, and cognitive functioning in a sense of the scar being a physical reminder of their illness and constantly trying to hide it [30].

A breast can be removed but this is only the beginning of a long road ahead of radiotherapy, chemotherapy and sociopsychological endurance. Body image and physical attraction is more noticed and criticized by the public than oneself and we tend to preserve this image to keep up with the standards set by societies to avoid such scrutiny and damaging judgments. Any negative reaction and comment from relatives or society towards a patient post mastectomy can go a long way affecting body-esteem which in turn affects mental health. Not one patient can withstand this battle on their own, the support and acceptance of partners, family members and society is needed to reach the finish line with the least physical and

psychologic damage possible [31].

Some women see mastectomies as a new life, being grateful to be alive, others even though they understand the need of the surgery for their survival, feel grief following the loss of the breast. Being an element of the female's body image, the breast represents beauty, femininity, attraction and more importantly motherhood [31]. Hence by removing a breast we are fragmenting this feminine concept robbing them from a sense of sexuality and nurturance [29]. Helping and guiding women to adapt to the disease, accept this new body image and enhance self-esteem should be a part of the recovery process. Interventions such as cosmetic treatments for the surgical scar, peer discussion groups, psychosocial programs, and physical therapy should be discussed with the patient and implemented for developing a positive body image and self-esteem as part of the road to recovery [27].

Hormonal imbalances

Hormonal imbalances are a consequence of chemotherapy, endocrine therapy and ovarian function suppression. Endocrine therapy and ovarian function suppression antagonize the estrogen effect and act on blocking the GnRH-FSH-LH axis. This is with great efficacy in treating breast cancer but comes with significant side effects.

One of the major side effects reported by women is menopausal symptoms. These include hot flashes, sweating and vaginal dryness that were greatly amplified using ovarian function suppression (OFS) compared to Tamoxifen alone. The SOFT trial that studied the added benefit of OFS also showed the reported side effects by women who received Tamoxifen alone versus Tamoxifen with OFS and as mentioned above, women in the second subgroups reported more menopausal side effects than the subgroups of women treated with Tamoxifen alone. It is important to note that these symptoms that are usually encountered after a certain age in women, are encountered in women at a young, pre-menopausal age and are intensified because of the continuous effects of the medications. These hormonal imbalances are also hard to treat and alleviate since the hormonal therapies that are usually prescribed to the women with menopause to decrease their symptoms are contraindicated in breast cancer.

In addition to the common menopausal symptoms, hormonal imbalances increase the risk of osteoporosis. In fact, estrogen re-

ceptor blockade and the decrease in estrogen production in breast cancer treatment specifically with aromatase inhibitors, lead to accelerated bone loss and an increased fracture risk with a reduction in quality of life [32].

Sexual dysfunction

Sexual dysfunction in breast cancer is directly linked to distortion in the self-perceived body image and to the hormonal effects of the treatment. It is also affected by the psychological status of the woman. With the increased survival in breast cancer and the improvement in its treatment, a greater focus was made on the women psychological well-being and quality of life, and the hypoactive sexual desire disorder has emerged as a real problem in women with breast cancer.

After breast cancer surgery, women tend to perceive a negative image of their bodies. Women find themselves less attractive and less feminine after mastectomy thus lose their sexual desire, report feeling unappealing and distance themselves from their partners. Hair-loss, also secondary to chemotherapy, worsen the perception of their image and make women feel further unattractive. This would place them in a vicious cycle, where depression plays a major role, further exacerbating the sexual dysfunction [33-35].

Sexual dysfunction is not only affected by the external appearance, many undesirable effects were linked to the decreased estrogen levels secondary to chemotherapy-induced amenorrhea and hormonal therapy. These include, decrease in sexual desire, vaginal dryness and insufficient lubrication leading to dyspareunia [36,37]. Women reported inability to achieve a healthy sexual function with inhibition of the sexual cycle from decrease in desire, to arousal, and finally failure to reach orgasm [38].

Infertility

Breast cancer ranks as the number one cancer in young women with child-bearing age. The advancements in treatment modalities improved the survival and the cure chances in these women, however not without another cost: infertility. In fact, the likelihood of women having a pregnancy after breast cancer is 60% less than in the general population. Women at the time of diagnosis think of cure and survival, and the impact of cancer treatment on fertility is often overlooked [39,40].

One of the most detrimental long-term side effects of breast cancer treatment is premature ovarian failure with subsequent infertility. As treatment of premenopausal women with BC frequently consists of gonadotoxic chemotherapy or prolonged endocrine therapy, oncofertility counseling becomes a crucial step in the care plan of women with breast cancer [40]. Breast cancer survivors find themselves denied one of the purest gifts of life, of becoming a mother. This has a great negative impact on their psychosocial lives, where they feel deprived of one of their nature-granted rights.

Fortunately, with the introduction of oncofertility approach, women now have the chance of becoming pregnant and giving birth after beating breast cancer. Fertility preservation starts by fertility counseling to the patients diagnosed with BC and about to be started on gonadotoxic chemotherapy or on long-term endocrine therapy. It begins by explaining the risks of infertility and premature ovarian failure to the patients and tackles their life-goals and wishes to become mothers [41].

Fertility preservation techniques include temporary ovarian function suppression with GnRH agonists throughout their chemotherapy thus reducing the risk of premature ovarian insufficiency. Added to this technique are the embryo and oocyte cryopreservation which lately became the standard strategies to prevent infertility. They consist of preserving oocytes and embryos for women who plan on getting pregnant. Nevertheless, these latter techniques are not without a cost, they present a significant financial burden to both the patients and health-care system, in addition to the risks faced by these women undergoing fertility surgeries [42].

Conclusion

Preserving mental health is as vital as curing the cancer itself. The multidisciplinary treatment approach from systemic treatment to local surgery exhaust breast cancer patients both physically and mentally. Although treatment advances have improved the survival rate in patients, it was at the cost of the psychological status of the women and their quality of life. Menopausal symptoms, mood and cognitive changes, dissatisfaction with body image, loss of the femininity and sense of sexuality, and more importantly loss of motherhood are just the tip of the iceberg of psychological changes a woman experiences on her road to recovery.

Shedding the light on the psychological impact has motivated societies and clinicians to help women survive their BC battle with-

out losing their identity. Helping and guiding women to adapt to the disease, develop self-esteem and accept this new body image has become a part of the recovery process. Interventions such as cosmetic treatments for the surgical scar, peer discussion groups, psychosocial programs, physical therapy, and fertility preservation should be discussed and implemented for developing a positive body image and self-esteem as part of her treatment process. Women should be able to win this war without losing any battle.

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