Review on Diagnosis and Treatment of Breast Cancer

T. Mangilal¹, K. S. K Rao Patnaik¹, Kishan Bookya²

¹Department of Pharmacy, UCT, Osmania University, Hyderabad-500007, Telangana, India
²Department of Pathology, ACSR Govt medical College, Nellore-524002, Andhra Pradesh, India

Abstract

Breast cancer is the second leading disease in women worldwide. Unfortunately, no adequate treatment available for progressing disease condition. In addition, severe pain experienced by the patients leads to negative psychosocial and physical impact on their lives. Patient-centered pain management therapies effectively working for controlling the pain caused by cancer. Early prognosis of breast cancer is more advisable. The risk of breast cancer depends mainly on menarche at an early age and menopause and first birth at late age. Ultrasonography and mammography are the most effective technique for the detection of cancer in pre and post menopausal women. Recent advancements in the treatment of breast cancer that include sentinel lymph node biopsy, partial breast irradiation, MRI, breast-conserving surgery, adjuvant systemic therapy and neoadjuvant systemic therapy. In addition; recently, minimal invasive techniques have been introduced, which include radiofrequency ablation, focused ultrasound ablation and cryotherapy. The present review article mainly discussing the diagnosing methods and treatment procedures of breast cancer to minimise the risk of severity in carcinoma patients.

Keywords: Breast cancer, pathogenesis, diagnosis, pain management

1 Introduction

Over 1.7 million new breast cancer cases are diagnosed globally, in which 25% of world women population suffering from breast cancer. Economically developing countries occupying 53% of breast cancer cases. According to the data of American Cancer Society, 521,900 breast cancer deaths have been reported in 2012. Asian countries largely burdened with breast cancer, representing 59% of world population. In addition, 39% of new breast cancer cases, 44% of breast cancer deaths, and 37% of five-year survivors have been reported (Table 1). Northern America and African countries representing 5% and 15% respectively. Several factors may increase the risk of prevalence breast cancer, which include age, gender, genetic factors, diet and alcohol, obesity, life style, physical activity, endogenous and exogenous factors¹.

1.1 Symptoms

A lump forms with no pain is the first symptom of early breast cancer. Severe pain due to involvement of ribs, muscles with increased chest movements occurred in the late stages. Mastectomy patients may have chronic neuropathic pain, which can be either post-mastectomy pain syndrome (intercostobrachial neuralgia), or scar pain (neuroma pain), or phantom breast pain or pain due to nerve injury³. A brachial or cervical plexopathy may be observed with radiotherapy at a site where an active painful skin lesion are present. Brachial plexus at the tumor region results severe pain and Horner’s syndrome, also causes sensory symptoms like numbness, swelling, paresthesia, dysesthesia and weakness of the arm⁴. Breast cancer survivors of 2-83 per cent suffer from lymphedema over the chest or arm⁵. The developmental secondary malignant growth (metastasis) is spread commonly from Breast to bones, lungs, brain and liver⁶, which often results headache, bone pain, and other symptoms in malignancy invasive areas⁷. The vertebral pain from nerve plexuses is relatively common in advanced metastasis condition⁸.

1.2 Epidemiology

Malignant breast cancer tumor is a major cause of death in women; it affecting 33% of all breast cancers in females. It
occupies second place in cancer mortality after lung cancer, middle aged (45-55yr) American women suffering in severe with breast cancer, which leads to death. According to the surveys, women are facing a lifetime risk with invasive breast cancer is 12.6%. In the United States, ten out of 80 females are suffering with breast cancer in their lifetime. Since 1988, the death rate due to breast cancer has been slowly declining after the steady increase for about 50 years. 25-30% of women unable to survive due to invasive breast cancer. Statistically, 70-75% of women will die with diseases other than breast cancer. Hence, diagnosing breast cancer in a woman is not necessarily the end of their life that most women think with fear of death, insufficient knowledge of invasive breast cancer, etc. Several surveys conclude that the mortality rate has been low in the age between 35-75 yrs. It means that very young and older people aggressively suffering with breast cancer lead to an increased mortality rates. Several recurrent cases (60-80%) have been occurring within the first 3 years, and it can exist up to 20 years.

### Table 1: Distribution of breast cancer cases, deaths and survivors in the world

<table>
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<tr>
<th>Continent</th>
<th>New breast cancer cases (%)</th>
<th>Breast cancer deaths(%)</th>
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### 1.3 Pathology of breast cancer

Most of the breast cancers (95%) are carcinomas, breast epithelial elements are mainly responsible for breast carcinoma. Patients suffering from two types of breast cancers, one is in situ carcinomas, and the second is invasive carcinomas. The in situ carcinomas remaining confined to one tissue, which either may arise from lobular or ductal epithelium with no invasion property (no extension of epithelial boundaries). The invasive (or infiltrating) carcinomas have a good potential for metastases, shows an extension of lobular or ductal malignancy beyond the epithelial borders; it ultimately leads to death.

### 1.4 Etiological Factors

#### 1.4.1 Age

Russel reported that breast cancer had been uncommon disease in 1920s, but the incidence of breast cancer gradually increases. By the time of 1990s, 20% of all women are suffering from breast carcinomas. Dumitrescu and Cotarla have reported that ten incidences of 100,000 women were younger (below 25 years), increased incident cases up to 100 times within 20 years. The reproductive hormones are mainly responsible for the pathogenesis of breast cancer during female reproductive periods. In addition, menopause and menarche contributions may increase the carcinogenic effects of sex hormones. Aguas et al reported that 15-20% risk of breast cancer reduced each year due to delayed menarche. However, late menopause at more than 55 years can be a risk factor. Increased estrogen exposure due to early menarche and late menopause can increase the risk of breast cancer. Furthermore, genetic and environmental factors play a significant role in the development of carcinomas.

#### 1.4.2 Gender

Males rarely suffer from breast cancer-only less than 1% of all patients. Several reasons for breast cancer in males, which include the presence of androgen, estrogen and progesterone receptors and Klinefelter’s syndrome.

#### 1.4.3 Genetic Factors

There are more probabilities of breast cancer if the patient had this disease in their family history. Russell reported that only 5% of breast cancers occurred due to the specific mutation. Several epidemiological meta-analysis studies revealed that only 12% of women patients have only one family member has been affected with breast cancer and 1% of patients have more than one relative were affected.

#### 1.4.4 Diet and Alcohol

Several factors play a role for the cause of breast cancer which include a low release of phyto-oestrogens due to low diet and high alcohol intake. Dumitrescu and Cotarla observed that an increased risk associated with progressive increase in daily alcohol consumption, in addition to that the risk increases with 9% on every incremental dose of alcohol (10g, approximately 0.75-1 L) after a normal alcohol intake (60g, 2-5 drinks) per day. Fatty food may increase the incidence of blood cancer: fat diet and well-cooked meat can increase calories intake due to presence of fat (approximately 35 to 40%) in it which leads to causing the mammary carcinomas effect. An increased secretion of oestrogen can be an incidence for the development of breast cancer, it is mainly occurred by taking fatty food contains rich in cholesterol can be acting as a precursor for the synthesis of several steroidal hormones and mainly oestrogens. The dietary fibre ingestion can inhibit an intestinal resorption of oestrogens by daily utilizing of 35-45g of dietary fibre. The higher probability of breast cancer can be seen in the Western world is due to lower consumption of dietary fiber, but less...
probable in Africa, South America and Asia where people have good amount of fiber content in their regular diet. Soya beans and vitamins have shown significant recovery from this disease; however, the precise mechanism has not been found.

1.4.5 Obesity, Lifestyle and Physical Activity

Several factors may influence the development of breast cancer; it includes exercise, diet and plasma concentration levels of hormones. Aguas et al\(^\text{16}\) reported that diet and exercise are the main factors which influence or increase the body weight leads to increasing the risk of breast cancer in post-menopausal women. Dumitrescu and Cotarla\(^\text{16}\) reported that breast cancer risk increased by 8% with each 5kg of weight gain. Fat present in adipose tissue is mainly responsible for weight gain and also acts as a source of estrogen, which are obtained from cholesterol.

1.5 Endocrine Factors

1.5.1 Endogenous

This is the most common cancer in infertile women and mothers who do not breast-feed their babies. An early first term pregnancy associated with early menopause and late menarche have found to be protective\(^\text{17}\). The women who did not bear children can have a lower risk of breast cancer due to low level of estrogen in women who had many children\(^\text{16}\).

1.5.2 Exogenous factors

Several meta-analysis regarding the long-term hormone replacement therapy (HRT) demonstrated that HRT is mainly responsible for the cumulative excess of breast cancer over women with 50-70 years of age\(^\text{16}\). Aguas et al\(^\text{17}\) reported that an increased risk of breast cancer associated with HRT, especially with current user has been administering estrogen and progesterin for five years. However, HRT has several advantages it includes decreased tension, headaches, depression and mood swings, relief of vaginal itching and dryness, as well as decreased risk of pathological fractures and osteoporosis\(^\text{17}\).

2 Diagnosing Breast Cancer: The Biopsy

The suspected breast cancer can be identified by three methods of diagnosis. Fine needle aspiration (FNA) is an unreliable diagnostic method because of indistinguishable ductal carcinoma obtained from invasive cancer and finally leads to a false result in negative values. Fine needle aspiration method is capable of removing cyst-like lumps visible on ultrasound or mammogram. Further biopsy is necessary due to false-negative results obtained by FNA. A Core needle biopsy is more reliable method than FNA in removing all types of cysts except obvious cysts. Core needle biopsies demand an excisional biopsy due to its high incidence of coexistent carcinoma in patients.

The 75-80% of excisional biopsies relatively are benign. Remaining 20-25% needed second surgeries to remove all cancerous tissues. An auxiliary lymph node in the most common predictor of survival and relapse\(^\text{22}\). Auxiliary recurrence in supra clavicular lymph nodes or internal mammary indicates a poor prognosis\(^\text{22}\). Level one auxiliary lymph node biopsy is known as a sentinel lymph node biopsy. It shows a positive predictive value (i.e 100%) with specificity of 100% and a sensitivity of 89%\(^\text{24}\). Non auxiliary regions consist of only 3% of all positive sentinel nodes. It shows ‘skip’ metastases reaching to level 2 and 3 auxiliary nodes with no involvement of level 1 nodes\(^\text{22}\). Therefore, the sentinel node biopsy is an expensive study can have survival rate of 85% in patients who are in first stage of breast cancer\(^\text{25-26}\). Infiltrating ductal carcinoma is the most common of all invasive breast cancers, which has poor survival rate. Medullary, papillary, tubular and mucinous have better prognosis methods, but capable of removing only 6% of invasive cancers\(^\text{25}\). In addition, blood vessel and peritumoral lymphatic invasion show much poorer prognosis. Progesterone and/or estrogen receptor positive tumors show a better response of hormonal treatment and prognosis than receptor negative tumors. DNA index can be measured by Flow cytometry and also having a better prognosis with diploid carcinoma cells than with aneuploidy\(^\text{27}\). Carnomas with high S-phase cells show a poor differentiation and prognosis\(^\text{28}\).

An increased tumor marker, CA 15-3 leads to metastatic breast cancer in many women. Several complications caused due to the presence of HER-2/neu oncoprotein (also called c-erbB-2), which include shorter time-to-relapse, shorter survival and an overall worse prognosis. Furthermore, this tumor marker potentially improves the health condition of cancerous patient with transfuzumab. The first USFDA-approval for conducting the blood test to identify the recurrence of breast cancer is denoted as CA 27.29. carcinoma cells than with aneuploidy\(^\text{27}\). Carnomas with high S-phase cells show a poor differentiation and prognosis\(^\text{28}\).

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In the recent study\(^\text{45}\) stated that the ratio for breast cancer death among the patients having high levels of total cyclin E in the tumor was higher than that of other biological marker, along with the presence of lymph node metastases (7 times higher), hormone-receptor status, and levels of HER-2/NEU. From 114 patients with Stage I breast cancer, 102 patients shown low levels of cyclin E had died due to breast cancer although under
the treatment since 5 years, but remaining 12 patients with a high level of low-molecular-weight cyclin E had died with breast cancer within that period. The hazard ratio for death in breast cancer patients when compared with high total cyclin E levels with low levels was 13.3 i.e., 8 times greater than that of a hazard ratio for other clinical and pathologic risk factors.

More recently, the prediction of gene-expression in young patients with DNA-microarray data is more powerful than previously standard systems, which is mainly based on clinical and histologic criteria. Patients with a good-prognosis signature had an overall 10-year survival rate of 94.6%. These data seem to indicate that currently used criteria misclassify a significant number of patients. These data suggests the distant sites of hematogenous metastasis are independent of lymphogenic metastases, and also such tumorigenic cell division is an early and inherent genetic property of breast cancer25. If verified, these studies should accurately identify patients most likely to benefit from adjuvant treatment30.

3 Treatments

3.1 Surgical therapy

Breast cancer surgery changed past 20 years ago. Due to the development of breast conserving therapy (BCT), huge women have the option of curing a cosmetically acceptable breast without giving of life31. The goal of BCT is to perform a cancer operation similar to partial mastectomy, lumpectomy and a cosmetically acceptable breast, with a low rate of reappearance in the cured breast25,32. All of the available data, including six randomized trials, show equivalent survival with BCT as compared to mastectomy24. The severe barrier spread over acquiring and practice of BCT are the risk of in-breast appearance. Most physicians oppose BCT and encouraging mastectomy if the risk of in breast reappearance has been more than 10 to 15 percent over the accomplishing 5 to 10 years, even after surgery and chemotherapy. BCT affords an acceptable mastectomy, an alternative in newly analyzed female patients (60-75%). In the past, the whole breast removed in the early stages of breast cancer instead of removing just the lump of cancerous cells. Now, Minn studied satisfactory results of mastectomies on 5, 500 women at the Mayo Clinic in Rochester35.

The choice of mastectomy can be a personal preference for most of women because it has very few contraindications. It also shows relative contraindications include multicentric tumors, large tumor (greater than 5cm) and collagen vascular disease36. It has been evidenced that breast conserving surgery is not a final option for all women patients. Mastectomy is the main choice of method when the tumor size exceeds 14cm and radiotherapy has been avoided in patients. Several studies explain the importance of an axillary lymph node dissection, mandatory for predicting the recurrence and survival27. Axillary and sentinel lymph node dissections are classified under traditional biopsy techniques, sentinel lymph node biopsy technique. The traditional dissection method has a standard procedure since several years but shows side effects such as lymphedema, seroma formation, sensory disturbances, poorer cosmetics, pain and infections38. On the other hand, the sentinel node biopsy clears the lymphatic drainage from a tumor with minimal side effects. now a days, this technique is considered as a best technique39.

3.2 Minimal invasive procedures

Breast conservation therapy has been a choice of treatment for early-stage breast carcinoma patients. Furthermore, sentinel lymph node biopsy helpful in predicting the status of an auxiliary lymph node without dissecting any element of auxiliary lymph node40-43. Recent developmental techniques such as focused ultrasound ablation (FUS), Percutaneous tumour excision and radiofrequency ablation (RFA) are used to remove the primary tumors with the least invasive procedures (open breast surgery).

3.3 Percutaneous Stereotactic Biopsy

Percutaneous stereotactic biopsy technique is used to treat benign and malignant lesions obtained in breast region44. These biopsy systems, which include Minimally Invasive Breast Biopsy (MIBB), Advanced breast biopsy instrumentation (ABBI) and Vacuum-assisted core sampling device (Mammatome), were used exceptionally in peritumoral purposes.

3.4 Radiofrequency Ablation

Radiofrequency excision can be beneficial in the treatment of primary or metastatic tumors of various organs such as lungs, central nervous system, liver, bones, pancreas and kidneys. this technique is mainly helpful to destroy the tumor with heat treatment45-47. RFA electrodes are penetrated into the tumor with a radio frequency of 15gauge and alternatively high frequency electric current (400-500 kHz) is also applied. The heat supplied to the tumor cell affects the fluidity of the cell membrane and the cytoskeleton proteins and outcomes in the interruption of cell replication by acting on a nuclear structure. This effect leads to irrevocable tumor eradication, as tumor cells are highly adaptable to heat than normal cells. The RFA focused tumor volume depends on applied tension (up to 200 W). Under imaging guidance, the RFA probe is penetrated into the center of the blister and a star-like chain of electrodes is delivered from the tip of the analysis. Target temperature (95°C) reached within 5 minutes of time, maintained same temperature upto 15 minutes to achieve complete ablation excision, and followed by one minute cool-down period. Sensors can be used to check the all temperatures during the process48. Various studies surveyed the benefit of RFA excision in the treatment of breast cancer. The procedure was well-approved under local anesthesia and sedation, but the investigators do not suggest...
the RAF as an alternative therapy to open surgery because the patients have a sedentary disease after application of the intervention\textsuperscript{49-52}.

### 3.5 Focused Ultrasound Ablation

Thermal tumor excision has also been calibrated with FUS. After annotation of the tumor in the breast, ultrasound can be done and rapidly build a significant rise in local temperatures up to 90°C by changing acoustic energy into heat. FUS excision heats the blister and causes cell ruith and tumor death\textsuperscript{53}. FUS is based on a 1.5-MHz ultrasound source. Tumor excision is checked through temperature analysis and skin monitors. Duration of FUS excision is usually 10 minutes. The major benefit of FUS over other ablative techniques is no need of skin incisions. However, this technique adversely effects the causing skin burns.

### 3.6 Laser Ablation

Laser ablation technique is well known identified as local treatment for breast cancer, produces heat at tumor region and causes malignant cell death and finally tumor destruction. Laser energy directly focuses to target site through a fiber optic probe inserted under imaging guidance. Various laser types have been surveyed and used for the thermal incision: the Nd:YAG laser (1064 d, 1, 320 nm), semiconductor diode laser (805 nID) and argon laser (488 and 514 nID). No extensive study about laser ablation has not been reported, but few studies observed that small size tumors have been ablated with negative results\textsuperscript{54}. After technical corrections, the success rate is increased enormously to 93\%\textsuperscript{55}.

### 3.7 Cryotherapy

Cryotherapy is a technique utilizing coldness, used to treat uncontrolled liver metastases formed at colorectal region\textsuperscript{56}. It consists of nitrogen or argon freezing system and a helium heating system. Seven probes are simultaneously involved in treating large tumors, the 470 probe inserted into a tumor through a tiny incision and scanned under imaging techniques such as ultrasound or MRI. After positioning of probe, Iceball is placed at the needle tip, which destroys the tumor and additional breast tissue present around the lesion. The constant monitoring of temperatures ranging from -185°C to -70°C is essential in each freeze cycle\textsuperscript{57-59}. It concluded that the cryotherapy has been a promising technique for early-stage breast cancer used along with local anesthesia\textsuperscript{60,61}.

### 3.8 Postoperative radiotherapy

Postoperative radiotherapy potentially reduces the risk of recurrence of breast cancer in women and also improves a breast cancer mortality rate, both will be achieved after mastectomy and breast-conserving surgery\textsuperscript{62}. Many patients shows fear of radiation therapy, but nowadays, well tolerated radiotherapy course available with a limited side effect, which works only the place where beams are focused. The main advantage of this therapy is that it will not cause any hair loss, lowering of immunity and nausea as like tumors irradiation in normal cancers.

### 3.9 Pain management

Pain management is a process of assessment and evaluation of critical pain and physiological condition of the patient by thorough evaluation of patient disease history. The approach of patients for the pain management depends mainly on the aetiology of pain. According to the WHO analgesic ladder, oral analgesics show an appreciable level of therapeutic effect for controlling of pain in patients with the highly carcinoma condition\textsuperscript{63}.

### 4 The Breast Health Global Initiative (Bhgi) Guidelines\textsuperscript{64}

BHGI, An international health alliance established in 2002, has developed evidence based guidelines to improve the breast health outcomes with minimal resources. These recommendations are made especially for low and middle resource countries.

- Cancer registries are required so that infection stage and treatment result can be measured.
- National breast cancer plans should characterize health care systems in which associations are made to outreach the rural and remote areas for diagnosing and treating the breast cancer at early stage.
- Proper training facilities should be provided for physician and health care staff, equipment availability and quality care initiatives that gauge utilization and clinical results.
- Conducting public awareness camps that facilitates an early detection of breast cancer
- Diagnostic methods, systemic therapy, surgical treatment, and palliative care should be integrated to improve the health services in multidisciplinary environments.

### 5 Conclusions

Breast cancer has been a major cause of death in women since few decades. Several factors are involved independently or in combination causing breast cancer. The aetiopathogenesis of breast cancer is associated with high mortality and morbidity, if patient unable to diagnose her disease in early stage. Therefore, early screening of breast cancer minimizes the risk of severity. In addition, careful surveillance is also needed for detection of disease recurrence.

Efforts should be made towards early diagnosing the disease and standardized treatment to reduce the rate of mortality in rural and backward areas due to breast cancer. The quality life of breast cancer survivors expanded incrementally due to viable
treatment methods accessible. In addition, persistent chronic pain has also been reduced with pain management therapy. Several adjuvant medications and analgesics are available to the patients. Satisfactory analgesic activity can be achieved with these medicines; however, pain relieving drugs caused few side effects. Further research is needed to minimize the side effects and adequate pain relieving actions for breast cancer patients.

6 Competing Interests

No

7 Author’s Contributions

TM carried out literature review and drafts the manuscript. KSKRP participated in collection of data. All authors read and approved the final manuscript.

8 References


