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BREAST CANCER MANAGEMENT

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ABSTRACT

Breast cancer has been recognised since antiquity, and as the disease's nature changed over time, so did the approach to treatment. Hippocrates classified breast cancer as a humoral illness in 460 BC, but following much research, it is now thought to have localised causes and systemic origins. Halsted radical mastectomy was the "established and standardised operation for cancer of the breast in all stages, early or late" for the majority of the 20th century.Recent discoveries on the biology of tumours and their behaviour raised the possibility that less invasive surgery could be just as successful as more involved ones. The scope of surgical resection in the breast and axilla was eventually further reduced with the use of adjuvant therapy, such as radiation and systemic therapy, ushering in an era of breast conservation.In an effort to shorten treatment times and minimise normal tissue harm, breast cancer radiation therapy has progressed from 2D to 3D conformal and accelerated partial breast irradiation. A proven method of treating breast cancer is systemic therapy, which includes biological agents, hormone therapy, and chemotherapy. The care of breast cancer today is predicated on the quickly developing and more comprehensive research on the cellular, molecular, biochemical, and genetic underpinnings of the illness.The task ahead is to leverage this understanding to forecast treatment outcomes, create new treatments, and quickly implement more cutting-edge biologic therapies.

INTRODUCTION

Breast cancer is a complex and diverse disease with varying biological behaviors. While surgery remains a cornerstone of treatment, numerous medical therapies have emerged. Effective breast cancer management relies on collaboration among specialists, including researchers, radiologists, pathologists, surgeons, radiation oncologists, medical oncologists, and psychologists. Through their collective efforts, significant advancements have been made in three key areas: local breast treatment, regional lymph node management, and systemic disease control, leading to improved patient outcomes.

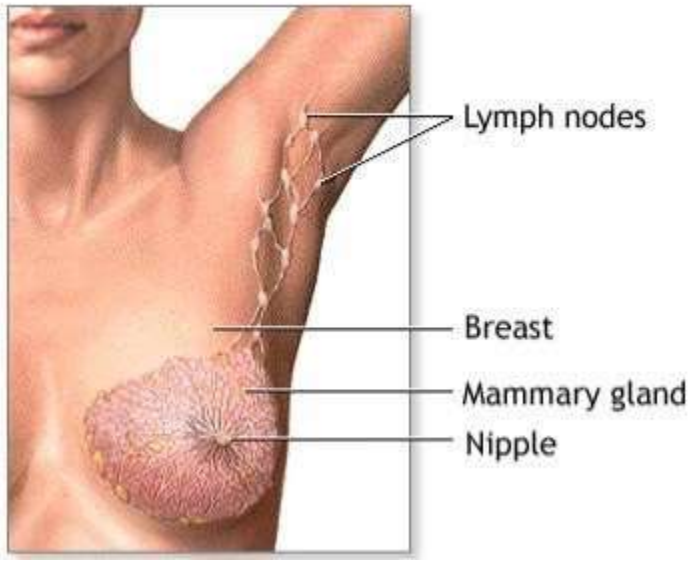


Fig.1. Breast Cancer.[22]

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HISTORY

Breast cancer has been documented throughout history, with the earliest recorded cases found in ancient Egyptian medical texts over 3,500 years ago. The Edwin Smith papyrus (circa 3000-2500 BC) describes eight breast cancer cases, noting no effective treatment, except for one instance of cauterization.[1] Ancient Indian texts (around 2000 BC) mention surgical excision, cautery, and arsenic compounds for treatment. In ancient Greece, Hippocrates (460 BC) attributed breast cancer to humoral imbalance, while Galen (131-203 AD) linked it to excess black bile.By the 16th century, techniques advanced. Andreas Vesalius introduced ligatures, and Jacques Guillemeau advocated for removal of the pectoral muscle along with the breast tissue. These early descriptions and treatments laid the groundwork for modern breast cancer management.Breast cancer has been documented throughout history, with the earliest recorded cases found in ancient Egyptian medical texts over 3,500 years ago.[2]

The Understanding of Breast Cancer Progression Evolved Significantly with key contributions from:[3]

1. Descartes (1596-1650), who proposed a lymphatic origin theory, later supported by John Hunter (1728-1793).
2. Henry LeDran (1757), who introduced the concept that breast cancer begins locally, then spreads to lymph nodes and enters circulation, suggesting early surgery could potentially cure the disease.
3. Henry Arnott (1871), who reaffirmed the local origin of breast cancer and championed curative surgery through en-bloc resection at the earliest stage.

These pioneers recognized the importance of axillary nodes and lymphatic spread, shifting the focus from humoral theories to surgical intervention, offering hope for a potential cure through early treatment.

Surgery :- The Halsted radical mastectomy, introduced in 1882, significantly reduced local breast cancer recurrence from 51-82% to 6%. However, this extensive surgery caused deformity, lymphedema, and sensory issues. By 1912, surgeons modified the procedure, preserving the pectoralis muscles, and by 1948, Patey substantiated this approach.Radical mastectomies declined from 20% in 1976 to 3.4% in 1981. McWhirter's 1948 report and Fisher's prospective studies (1989) pioneered breast conservation and adjuvant radiation therapy.[4]

Surgical Management of Operable Breast Cancer Involves

1. Primary tumor treatment: mastectomy or lumpectomy.
2. Regional lymphatic management: lymph node dissection or sentinel lymph node biopsy.

For locally advanced breast cancer, neoadjuvant chemotherapy reduces tumor bulk, followed by:

1. Breast conservation therapy.
2. Modified radical mastectomy (MRM).[5]

Radiation therapy:- By the 20th century's start, radiotherapy proved effective in treating breast cancer.[6] Pfahler (1932) reported 80% 5-year survival in early-stage patients. Keynes (1937) achieved similar results using implanted radium needles. McWhirter's work (mid-20th century) showed simple mastectomy plus radiotherapy matched radical mastectomy's survival rates.[7]

Landmark Studies

1.Atkins et al. (1972): First randomized trial comparing conservative surgery + radiotherapy to radical mastectomy.
2.Fisher et al.: Prospective study proving breast conservation therapy with radiation equals radical surgery.

Recent Findings:- Danish, Canadian, and second Danish studies,Local control impacts survival; eradicating locoregional metastases improves outcomes.

Radiotherapy Advancements:- 1.2D to 3D Conformal Radiotherapy (3DCRT)

2.Accelerated Partial Breast Irradiation (APBI)[8]

Systemic Therapy

There Are Three Primary systemic treatment options for breast cancer:

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1.Endocrine Therapy (ET): For patients with estrogen and/or progesterone receptor-positive tumors (approximately 2/3 of cases).
2.Chemotherapy (CT).
3.Biological Therapy (BT): Targeted agents focusing on specific molecular targets in cancer cells and their environment.

These modalities provide effective systemic management of breast cancer.[9]

Hormone therapy:-By the 19th century's end, Thomas Beatson showed breast cancer's hormonal dependence through tumor regression after surgical oophorectomy. Later, adrenal and pituitary gland surgeries confirmed this. The discovery of estrogen receptors in breast tumors solidified hormone dependence.[10]

Today, medical endocrine therapies have replaced surgical ablation:
1.Tamoxifen (estrogen antagonist) replaced oophorectomy.
2.Aromatase inhibitors (anastrozole, letrozole, exemestane) replaced adrenelectomy.
3.LHRH agonists replaced hypophysectomy.[11]

Hormone receptors (ER, PR) and HER2 status guide therapy choices:-
1.ER/PR-positive patients: Hormone therapy (tamoxifen, aromatase inhibitors, ovarian suppression) + chemotherapy.
2.HER2-positive patients: Anti-HER2 targeted agents improved prognosis.

New Developments:- Fulvestrant, a steroidal estrogen receptor antagonist, for advanced breast cancer post-endocrine .[12]

Chemotherapy :- Chemotherapy's introduction in the 1950s-60s revolutionized treatment for advanced solid tumors and hematologic neoplasms. In breast cancer, initial single-agent chemotherapy (e.g., cyclophosphamide, methotrexate) yielded 0-38% response rates. Combination chemotherapy emerged:
1.Cooper's regimen
2.Bonadonna's CMF protocol (Cyclophosphamide-Methotrexate-5-Fluorouracil), introduced in 1976
CMF became the gold standard, but anthracycline-based regimens replaced it in the 1990s. A 2005 EBCTCG review showed: - Anthracyclines reduced breast cancer death rates by 38% (under 50) and 20% (50-69)

- Adding taxanes to anthracyclines improved outcomes[13]

Pivotal Trials
1.CALGB 9344 and NSABP B-28: Paclitaxel after AC (doxorubicin+cyclophosphamide)
2.BCIRG 001:TAC(docetaxel+doxorubicin+cyclophosphamide)outperformed FAC (5- fluorouracil+doxorubicin+cyclophosphamide)

These advancements significantly improved early-stage breast cancer treatment.[14]

Targeted Therapy:-Targeted therapies revolutionized cancer treatment by selectively inhibiting mechanisms driving cancer growth, invasion, and metastasis.

1.Imatinib (BCR/ABL TKI): Proved targeted therapy's efficacy.
2.Tamoxifen: First targeted therapy in breast cancer.
3.Trastuzumab (HER2/neu monoclonal antibody): Cornerstone in HER2+ breast cancer treatment. HER2 overexpression (20-25% of breast cancer patients) leads to aggressive tumor behavior. VEGF
receptor family is another crucial target in angiogenesis and metastasis.[15]

Breakthroughs
1.Bevacizumab (VEGF monoclonal antibody): Approved with paclitaxel for HER2-negative metastatic breast cancer.
2.Lapatinib (dual HER1/2 TKI): Active in trastuzumab-pretreated metastatic breast cancer.
3.Combination therapy: Lapatinib + trastuzumab effective beyond trastuzumab progression.[16]

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Emerging Areas
1.PARP inhibitors (poly ADP-ribose polymerase inhibition).
2.Novel antibodies (pertuzumab, T-DM1).
3.Irreversible TKIs (neratinib, BIBW 2992).
4.Downstream signaling inhibitors (mTOR, TORC ½, PI3K/Akt).
5.Receptor cross-talk inhibitors (estrogen receptor, insulin-like growth factor receptor).[17]

Future Research Directions
1.Evaluating novel agents in HER2+ breast cancer.
2.Investigating combination therapies.
3.Targeting downstream signaling and receptor cross-talk.[18]

Triple Negative Breast Cancer:-Triple Negative Breast Cancer (TNBC) lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) expression, making it aggressive and challenging to treat. However, some patients respond to chemotherapy, emphasizing the need for optimized regimens.[19]

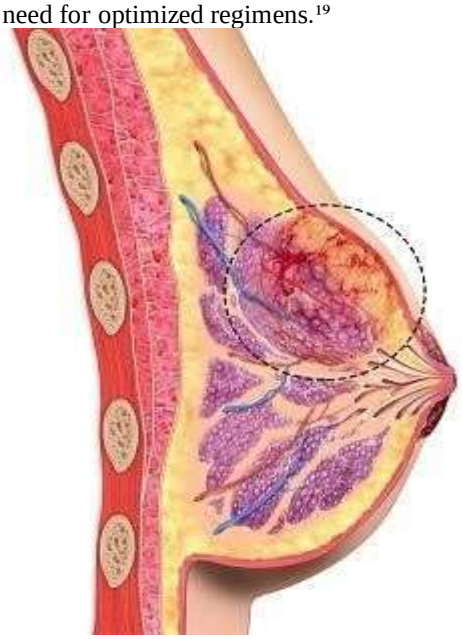


Fig.2.Triple Negative Breast Cancer [23]

Established Treatments
Taxane-based regimens (Level 1 evidence)

Emerging Approaches
1.Epothilones (microtubule-stabilizing agents) show promise in TNBC.
2.Ixabepilone (epothilone B analogue) is effective for TNBC.
3.ombination therapy: Ixabepilone + capecitabine outperforms capecitabine alone in taxane-sensitive/resistant ER-negative tumors.

New Horizons:-PARP inhibitors (in clinical trials for TNBC)Optimizing chemotherapy and exploring targeted agents are crucial in combating TNBC.

Metastatic Breast Cancer:- Managing metastatic breast cancer (MBC) lacks standardized treatments, unlike early-stage breast cancer. Guidelines:

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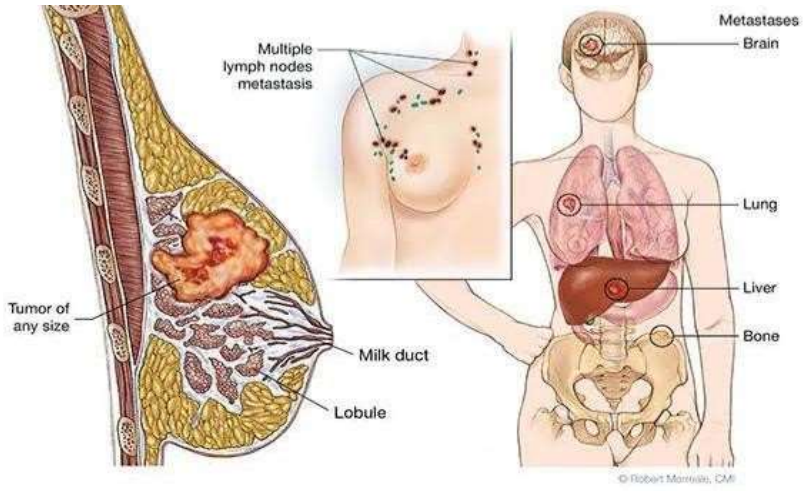


Fig.3.Metastatic Breast Cancer [24]

Hormone Receptor-Positive MBC
1.Endocrine therapy preferred, unless aggressive disease or resistance suspected.
2.Individualize treatment based on patient profile, co-morbidities, and tumor biology.
3.Premenopausal: Tamoxifen + ovarian ablation.
4.Postmenopausal: Third-generation aromatase inhibitors.

HER2/Neu-Positive MBC
1.Trastuzumab (Herceptin) with/without chemotherapy.
2.Lapatinib + capecitabine for patients progressing after trastuzumab.

Chemotherapy Approach
1.Sequential single-agent therapy preferred over combination chemotherapy.
2.Reduced toxicity and improved quality of life. Key considerations:
1.Patient safety profile.
2.Tumor biology
3.Co-morbidities.
4.Quality of life[20,21]

CONCLUSION

Breast cancer management has evolved due to advancements in understanding its pathogenesis, genetics, molecular biology, and technology. Today's approach integrates these disciplines. Despite progress, many women face recurrence and metastasis, while others receive unnecessary adjuvant therapy.

Future Directions
1.Recognizing tumor heterogeneity and molecular profiles.
2. Developing targeted therapies with increased efficacy and reduced toxicity
3.Personalized medicine: Identifying patients who will benefit from specific treatments.

Challenges Ahead
1.Predicting therapeutic outcomes.
2.Rapidly integrating novel biologic therapeutics into clinical practice.

The goal: Tailored treatments, improved outcomes, and enhanced quality of life for breast cancer

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