**Clinicopathological Insights of rare Breast Carcinoma with characteristic diagnostic features of medullary cancer and medullary features : A mini-comprehensive literature review of Medullary breast cancers.**

**ABSTRACT**Medullary breast carcinoma (MBC) is a rare histological subtype of invasive breast cancer, accounting for less than 5% of all breast malignancies and presents with a unique clinical paradox. Despite its aggressive histopathological features such as high-grade nuclei, prominent lymphoplasmacytic infiltration, and syncytial growth patterns ,it often demonstrates a more favorable prognosis compared to other high-grade breast cancers, particularly invasive ductal carcinoma (IDC). This paradox has drawn significant interest in understanding its unique biological behaviors. It bears varying morpho-pathological and immunological resemblance to medullary-like carcinoma, oligodendrogliomas, seminoma, dysgerminoma, hairy cell leukemia and breast cancers like Basal-like breast carcinomas (BLBCs).

MBC is frequently triple-negative, lacking expression of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu, which limits the applicability of targeted hormonal or HER2-directed therapies. However, the presence of dense immune infiltration and associations with BRCA1 mutations suggest potential responsiveness to immunotherapy and DNA-damage targeting strategies.

This review explores clinicopathological characteristics, diagnostic challenges, molecular profile, and evolving therapeutic approaches in the management of MBC. A better understanding of its underlying biology may pave the way for more effective, individualized treatment options and improved clinical outcomes.

**Keywords:** Medullary breast carcinoma, Medullary features in breast cancer, Estrogen, Progesterone, Histopathology, biomarkers.

**INTRODUCTION**

Globally, breast cancer (BC) in women predominates as the most ubiquitously diagnosed cancer and records the highest fatality from malignancy [1]. Albeit considerable research being done in the group of prominent breast cancers, the contrary has been the case with the rarer subtypes. However, with the improvement of diagnostic and staging technologies, these tumor types are increasingly being identified [2]. BC can be classified based on several systems consisting of clinical stage and grade, and are built on imaging studies (e.g. Mammography, Ultrasound, MRI, PET/CT scan), molecular patterns (protein expression and gene mutation), and morpho-pathological classifications [3]. In the morpho-pathological class of invasive division, invasive ductal carcinoma (IDC) aggregates 55-80% , followed by invasive lobular carcinoma(10%), and the entire rare subtype aggregates 10-35% of all cases[2].

Medullary breast carcinoma (MBC) is a distinct and seldom-seen subtype of breast cancer which poses unique diagnostic and therapeutic challenges that was first reported in 1949 by Moore and Foote where it was described as “Medullary like carcinoma” [4]. It makes up less than 5% of Invasive ductal carcinoma and has been reported to have a better prognosis than IDC [5][6]. The rarity of this tumor, only recorded in literature by case reports and limited systemic review studies published, necessitates a thorough review of literature to ascertain what is in current knowledge. Typically, the tumor presents as triple-negative breast cancers (TNBC) on immunocytochemistry(IHC) characterized by negative estrogen receptor (ER), progesterone receptor (PR), and Human Epidermal growth factor receptor-2 (HER-2), along with a high level of TP53 proteins due to frequent p53 mutations. Additionally, they fall under the basal subtype of mammary epithelial cell lineage [7][8]. Less than 5% of all invasive breast cancers have a unique histological subtype with very strict criteria for diagnosis, that includes complete circumscription, syncytial growth pattern of at least 75% of the tumor, intermediate to high nuclear grade, associated diffuse lymphocytic infiltrate, and a lack of intraductal components or glandular differentiation [9].The 2019 World Health Organization (WHO) updated the classification of medullary carcinoma under the umbrella term “carcinomas with medullary features,” including atypical medullary carcinoma and invasive carcinoma of no special type with medullary features [10].**Table 1** showed summarized the comparison between a pure medullary carcinoma and medullary-like carcinomas. They are both subclassified into BRCA and non-BRCA subgroups. Among the BRCA1-associated breast cancers, 7.8% to 19% are medullary carcinomas, and 35% to 60% show the presence of medullary features [11][12].A high incidence of TP53 gene mutation also presents in the medullary carcinomas[7].Array-based comparative genomic hybridization analysis demonstrates a recurrent pattern of chromosomal alterations in medullary carcinoma, including 1q, 8q, 9p, 10p, and 16q gains; 4p and X losses; and 1q, 8p, 10p, and 12p amplicon.[13]

**Table 1** : **Comparison between Pure Medullary Carcinoma and Medullary-like Breast Carcinomas.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Feature** | **Pure Medullary Carcinoma (PMC)** | **Medullary-like Carcinoma (Atypical/Mixed)** | **References** |
| Definition | A distinct breast cancer subtype meets all histopathological criteria(Invasive Ductal CA). | Tumors that share features with PMC, but do not meet all diagnostic criteria. | [9] |
| Histopathology | Sheets of high-grade pleomorphic nuclei. Dense lymphoplasmacytic infiltrate,  Well-circumscribed margins - Minimal/no desmoplasia .No glandular/tubular structures.  >75% syncytial growth | Partial presence of PMC features (e.g., <75% syncytial pattern, more desmoplasia, focal gland formation) | [9, 10] |
| Immunophenotype | Commonly triple-negative (ER-, PR-, HER2-); basal markers (CK5/6, EGFR) often positive | Frequently triple-negative; basal marker expression more variable | [7] |
| Genetics | Strongly associated with BRCA1 mutation; homogeneous basal-like gene expression profile | May or may not be BRCA1-associated; more heterogeneous genetic profile | [11, 12] |
| Prognosis | Generally favorable; lower recurrence and metastasis despite high-grade appearance. | Intermediate prognosis—better than typical high-grade IDC, but worse than PMC | [7, 10] |
| Clinical Relevance | May not require aggressive therapy due to good prognosis | Treated more aggressively due to uncertain behavior | [7,10] |

There is need to highlight the relationship and similarities among medullary carcinoma, basal-like breast carcinomas, and carcinomas with the possible link to germline BRCA1 mutations. The are few studies that documented evidence of the existing strong relationship between Medullary Carcinoma, Basal-like Breast Carcinomas, and BRCA1-associated Breast Cancers.

They form clinically and biologically interconnected triad, while each has distinct diagnostic criteria, sharing overlapping features in morphology, immunophenotype, and molecular biology.

Medullary carcinoma is a rare histological subtype of invasive breast cancer, typically presenting with high-grade, poorly differentiated tumor cells arranged in syncytial sheets, dense lymphoplasmacytic infiltrate, and well-circumscribed, pushing margins [14, 15]. Despite these aggressive features, medullary carcinoma paradoxically carries a relatively favorable prognosis compared to other high-grade breast cancers [14].

The Basal-like breast carcinomas (BLBCs), defined by gene expression profiling, commonly exhibit a triple-negative receptor status (ER-neg, PR-neg, HER2-neg) ,basal cytokeratin (CK5/6, CK14) and epidermal growth factor (EGFR) positivity[14][15]. They are histologically high-grade, with frequent necrosis and a pushing invasive front that often resembles medullary carcinoma [16]. Notably, gene expression studies have shown that many medullary carcinomas cluster within the basal-like subtype, suggesting that MC is a distinct morphological variant of BLBC [17][18].

Classical medullary breast carcinoma (MBC) has recently been recognized to be part of the basal-like carcinoma spectrum, a feature in agreement with the high rate of TP53 mutations previously reported in MBCs [7].There is high expression level of estrogen receptor (ER), progesterone receptor (PR), ERBB2(Erb-B2 receptor tyrosine kinase 2), TP53, cytokeratin (KRTs) 5/6, 14, 8/18, EGFR and KIT in Medullary CA [10].BRCA1-associated breast cancers, arising in patients with germline BRCA1 mutations, frequently display a basal-like phenotype as well, and are often triple-negative and express basal cytokeratin, with histopathologic features that may mimic medullary carcinoma, including high-grade nuclear features and lymphocytic infiltrates [19]. In fact, medullary carcinoma is more commonly observed among BRCA1 mutation carriers than in the general breast cancer population [19]. Molecular analysis of the three subtypes (MC, BLBC, and BRCA1-associated cancers) share common pathways involving defective DNA repair and homologous recombination. BRCA1 is a key gene in this pathway, and its loss contributes to genomic instability, a hallmark of basal-like and BRCA1-related tumors.

The sporadic form of BLBCs often exhibit BRCA1 dysfunction through promoter methylation or other mechanisms [16, 19]. Clinically, this overlap is relevant for therapy, while basal-like and BRCA1-associated tumors tend to have a poorer prognosis due to their aggressive nature. They are particularly sensitive to platinum-based chemotherapy and poly(ADP-ribose) polymerase(PARP-2)inhibitors, which target DNA repair defects. In contrast, accurately diagnosed medullary carcinoma, despite its basal-like features and triple-negative status, often shows less aggressive clinical behavior, making it a potential candidate for de-escalation of therapy [14][15][16]. In summary, the medullary carcinoma can be considered a histologic variant within the basal-like molecular class of breast cancer and is frequently seen in the context of BRCA1 germline mutations. This triad highlights the importance of integrating histopathological, molecular, and genetic insights for personalized diagnosis and treatment strategies in breast cancer. Basal-like carcinomas (BLCs) were characterized by a specific immunophenotype that was negative for ER, progesterone receptor (PR) and ERBB2, and positive for cytokeratin (KRT) type 5/6, KRT-14 or KRT-17, epidermal growth factor receptor (EGFR) and KIT [16][17]. Medullary breast cancers tumors are generally triple negative and typically arises from supporting stromal cells of the breast [18].A reclassification into typical medullary carcinoma (TMC), atypical medullary carcinoma(AMC), and non-medullary carcinoma (NMC) can be relevant for therapeutic and academic purposes[19][20].

The criteria of TMC subtypes are[9][21][22]:

i. Syncytial growth pattern of poorly differentiated tumor cells with a high mitotic rate.

ii. Prominent lymphoplasmacytic reaction with a circumscribed microscopic appearance of inflammatory reaction, involving 75% of the periphery and must be present diffusely throughout the substance of the tumor.

iii.Absence of glandular or fatty breast tissue should be found within the invasive portion of the tumor .

The Atypical category resembles the usual classic case, which must have at least 75% syncytial growth without the other features like circumscription and lymphoplasmacytic infiltration [9].

Additionally, this review aims at highlighting the morphology, clinicopathological features of reported cases thus far, mediating the education of physicians and providing one-source updated findings to enable and increase the likelihood of their identification, thereby increasing interobserver reproducibility. Finally, the body of work is aimed at reducing MBC’s potential to be mistaken for IDC or other tumor types with similar histopathological features with unfavorable prognosis.

**EPIDEMIOLOGY**

A SEER 1988-2004 study of medullary breast cancer data shows 72% white, 19.7% Black, 6.8% Asian, 1% Native American, 0.5% others, with median age of 50, median size of 22mm, 56% ER negative and 58.4% PR negative[23][24][25].Tumor grade was high (III–IV) in 50.7% of patients and unknown in 43.2%. The ER and PR negative are 56.8% and 58.4% respectively and ER and PR positive 16.3 and 14% respectively [23][24][25][26].The medullary and medullary-like tumors fall into the basal-like molecular subtype, which has frequent BRCA1 mutations, protein deficiency ,extensive axillary lymph nodes involvement and variable histological findings [23][24][25][26].

MBC is almost entirely seen in women. It is common in younger patients within the ages of 45-54 years [1][7][9]. When ethnicity is considered, a higher incidence in Japanese and Black women compared to White women is noted [12][26][27][28].This is congruent with the fatality rates seen within this ethnic group. In a study conducted by Martinez et al., though they were not able to control for confounding factors like socioeconomic status and lack of access to health care, they reported an 84% increased risk of death due to MBC in Black women when compared with White women[12][28][29].

## **PATHOLOGY**

Medullary Breast Cancer is defined by WHO as a well-circumscribed, invasive carcinoma, composed of poorly differentiated cells, arranged in sheets, without gland formation. Collagenous stroma is usually scant, and there is a very prominent lymphoplasmacytic infiltrate [7]. Several classifications have been used for subtyping. In 1977, Ridolfi et al., in an effort to come up with a more stringent criteria for medullary carcinoma diagnosis, reclassified MBC into typical MBC and atypical MBC and in so doing unearthed the significant prognostic advantage the former had over the latter, as well as among all the typical breast cancer [11][12][30][31][32].However, Ridolfi et al.’s criteria remain the most widely recognized and employed [8][31][32]. The subtypes are grouped based on 5 criteria; when all five criteria are observed, it is termed typical medullary carcinoma, whereas the presence of some but not all, is referred to as atypical medullary carcinoma. Typical MCB are tumor type which strictly adhere to the following criteria:

1. Syncytial pattern of growth greater than 75% [7][14][15][31].
2. Predominant mononuclear (lymphocyte and plasma cells) infiltrate [7][14][16][32].
3. High nuclear grade carcinoma cells (nuclear pleomorphism) [7][33][34].
4. Well-circumscribed margins [9][33][34].
5. The lack of micro glandular patterns of intraductal component [9][35].

In recent years, WHO has coined the term “Carcinoma with Medullary features” to refer to all atypical MBC and invasive carcinoma of No special types with medullary features [11][17][33].

In 2012, the World Health Organization (WHO) refine the classification by grouping medullary carcinomas, atypical medullary carcinomas and carcinomas of no special type with medullary features under the main class as Carcinomas with medullary features [11][32][33].In 2019, WHO further revised the name of the class from Carcinomas with medullary feature to Tumor-infiltrating lymphocytes (TIL)-rich invasive BC of no special types (TIL-rich IBC-NST) [17][18][33].Furthermore, many studies have reported numerous classification using immunoprofile findings and other associations that could be required for patients survival such as strong association and high incidence of MBC in women with familial BRCA1 mutation [7, 15, 19]. Additionally, the high prevalence of TP53 proteins is also noted due to the frequent TP53 mutation [7][31][32].MBC is considered a subtype of Triple negative Breast Cancer (TNBC), with 82% of patients with negative findings upon immunohistochemical staining for Estrogen receptor (ER), Progesterone receptor (PR), and Human Epidermal growth factor receptor-2 (ERRB2, formerly HER2/neu) which is characteristic of TNBC, while the other 8% of these patients do present with HER2+ [18][33]. MBC also associated with high expression of basal-like markers, such as cytokeratin's 5/6 and 17, as well as EGFR and markers for myoepithelial cells in the breast[17][34].TNBC is known to have a poor prognosis with a shorter survival time at fatality rate of 40% within 5 years, but MBC which fall in the spectrum of TNBC tumors happens to be an exception to this rule[1][17] .Though, MBC in a similar fashion like TNBC and the basal-like breast cancer do present with highly malignant histopathological findings(see Images 1 -6), advanced grade and larger tumor size. As a matter of fact, upon gene analysis 95% of MBC falls under the basal like phenotype[10][35].However, MBC has a good prognosis and high overall survival rate[31][36].

**Clinical and histological manifestations**

A large majority of patients, on physical examination, present with a palpable, rapidly growing, large, soft, mobile mass typically located in the upper outer quadrant of the breast [8][24].The rapid growth is partly attributable to the extensive hemorrhage often seen within the tumor on gross pathological examination. Most patients present with a unilateral lesion; however, approximately 3–18% have bilateral breast involvement, a presentation more typical among individuals with a known family history of the disease [18][19][36]. Some patients also present with axillary lymph node involvement, indicating metastasis, which is associated with poorer outcomes. Most published studies report a lower incidence of axillary lymph node involvement in patients with classic medullary carcinoma (19% to 46%) compared to those with atypical medullary carcinoma (30% to 52%) or invasive ductal carcinoma (29% to 65%) [8][24][25][26]. Patients with lymph node–positive MBC have shown a significantly lower 10-year overall survival compared to those with node-negative disease (58.8% vs. 97.1%) [25].

Patients with triple-negative breast cancer (TNBC) and a family history of breast cancer are often present with ipsilateral or bilateral dual breast lesions. When palpated, MBC may feel sharply defined and can sometimes be mistaken for fibroadenoma [21][24][37]. Grossly, MBC appears as a round, well-delineated tumor with a nodular architecture and lobulated border[38][39]. On sectioning, the mass often swells outward and appears as a homogeneously firm, gray mass with moist, glistening surfaces, sometimes interspersed with hemorrhagic zones and areas of necrosis. It tends to grow expansively, protruding on sectioning; a feature that helps distinguish it from scirrhous carcinoma, which is infiltrative and exhibits a sunken surface on gross examination [4][14][40][41]. Histologically, MBC is characterized by coalescing sheets of large tumor cells with indistinct cytoplasmic borders, prominent mitotic figures, and high nuclear grade, accompanied by a dense mononuclear lymphocytic infiltrate[41][42]. Smudged cells are also frequently observed in MBC [7][16][41][42].

**Diagnosis**

Previously, the diagnosis of Medullary Breast Carcinoma (MBC) was based solely on histomorphological characteristics of biopsied samples[see Images 1-6].However, the diversity in clinical outcomes and the poor reproducibility of diagnoses between pathologists necessitated a more stringent methodology that was initially proposed by Ridolfi et.al. and later modified by other researchers over the years [2][8][9]. It is noteworthy to remember that MBC could shares similar histopathologic pattern(“fried egg appearance”) with Oligodendroglioma, Hairy cell leukemia, Seminoma and Dysgerminoma. This diagnostic confusion has also been observed in radiographic imaging, where MBC shares similar features with fibroadenoma [22][23][24].Magnetic Resonance Imaging (MRI) is a secondary diagnostic tool that has proven valuable when used in conjunction with other modalities for suspected cases of MBC. However, additional techniques are increasingly being employed to ensure diagnostic accuracy, particularly immunohistochemistry and genetic profiling [10][11[12]. Molecular and cytogenetic testing is especially recommended for younger patients, individuals with a family history of breast cancer, those with genetic syndromes associated with breast cancer, and patients whose test results could influence treatment strategies (e.g., consideration of prophylactic mastectomy) [7][11]. Approximately 15% of tumors in BRCA1 mutation carriers exhibit a distinctive immunoprofile, which may include negativity for CK5/6, CK14, EGFR, HER1, and p53, along with negativity for ER, PR, and HER2 [7][18][19].In a study conducted by Alfaro et al., a distinct microscopic signature associated with MBC was reported, which distinguishes it from atypical and triple-negative breast cancers with tumor-infiltrating lymphocytes (TILs)[27]. This signature feature is the peripheral localization of immune cells predominantly CD20 positive, with a notable spatial separation between them and the tumor cells [27] .

Radiologically, on mammography, MBC appears as a uniformly dense, round or oval, non-calcified mass with indistinct or circumscribed margins[Image 7]. On sonography, it presents as a circumscribed mass with an inhomogeneous hypoechoic texture, which may be oval or lobular, and with either regular or irregular margins[Image 7][22][23][24]. On MRI, MBC typically appears as an oval or lobular non-calcified mass with distinct or obscured margins, showing rim enhancement with or without enhancing internal septations on contrast-enhanced images[Image 8][24].

A close-up of a human body

AI-generated content may be incorrect.

**Image 1**:The gross image of a well circumscribed capsulated grayish tumor moderate in size. The mass bear resemblance to fibroadenoma, fibrocystic changes or Benign phyllodes tumors. Inset is a fixed highly necrotic tissue.

**Source:** Dr. Ikenna Alban Mgbehoma (B.Sc., MD, FMCPath),LASUTH, Lagos, Nigeria(2023).

Histological Slide showing the syncytial growth pattern of MBC 


**Image 2**: Medullary pattern in syncytial fashion of well-defined multinucleated sheet of cells that are not separated into individual cells(Low power view H&E X 40)

**Source**: Dr. Ikenna Alban Mgbehoma.(B.Sc., MD, FMCPath).,LASUTH, Lagos, Nigeria(2023).

A close-up of a cell

AI-generated content may be incorrect.

**Image 3**:Histopathological image shows a monotonous sheet of cells (small round blue cells) with scanty cytoplasm and round nuclei, in syncytial pattern consistent made of lymphoplasmacytic infiltrate resembling neuroendocrine tumor ,Seminoma, Dysgerminoma and Lymphomas .

**Source**: Dr. Ikenna Alban Mgbehoma(B.Sc., MD, FMCPath).,LASUTH, Lagos, Nigeria(2023).

A close-up of a purple cell

AI-generated content may be incorrect.

**Image 4**: High grade invasive breast carcinoma of no special type with highly dysplastic nuclei and lymphocytic infiltration. (High power view H&E X 100).

**Source**: Dr. Ikenna Alban Mgbehoma(B.Sc., MD, FMCPath),LASUTH, Lagos, Nigeria(2023).

A close-up of a purple and white tissue

AI-generated content may be incorrect.

**Image 5**: Poorly differentiated breast cancer with non-monotonous dysplastic nuclei and lymphocytic infiltration bear resemblance to Lymphoma.(High power view H&E X 100).

**Source:** Dr. Ikenna Alban Mgbehoma(B.Sc., MD, FMCPath),LASUTH, Lagos, Nigeria(2023).

A close-up of a cell

AI-generated content may be incorrect.

**Image 6**: Immunohistopathological image of a breast tumour showing well-circumscribed soft tissue stromal neoplasm, with pushing border located adjacent to adipose tissue.

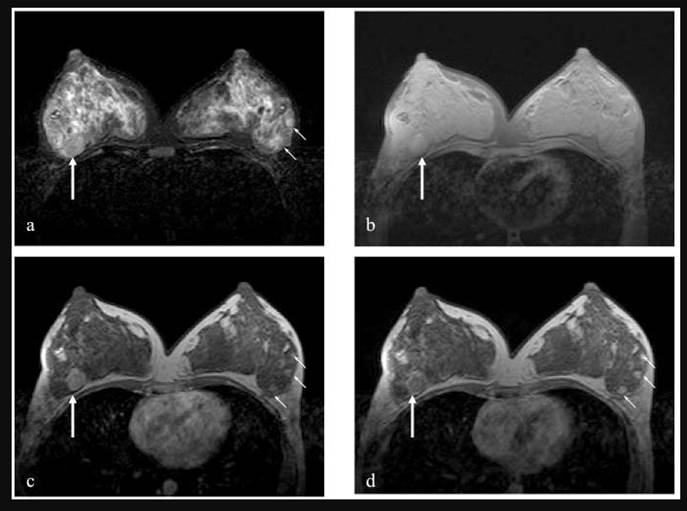
**Source**: Dr. Ikenna Alban Mgbehoma.(B.Sc., MD, FMCPath),LASUTH, Lagos, Nigeria(2023).

A close-up of a ultrasound

AI-generated content may be incorrect.

# **Image 7**: (a) Mammogram of a medullary carcinoma showing a uniformly dense, round or oval, non-calcified mass with indistinct or circumscribed margins (b) Ultrasound scan of the medullary carcinoma with well circumscribed hypoechoic posterior enhancement with regular margin[24][25].

**Source**: PubMed



**Image 8**:Breast MRI series (a to d) of medullary carcinoma (long white arrows).

(a) Isointense tumor image on the T2-weighted STIR axial sequence.(b) isointense on the T1-weighted fat-saturated axial sequence. (c) Homogeneous enhancement in the early dynamic post-gadolinium sequence and (d) Delayed peripheral enhancement showing malignant lesion. Images a, c and d have gradual homogeneous enhancing fibroadenomas (short white arrows) [22][23][24].

**Source**: PubMed

**DIFFERENTIAL DIAGNOSIS**

**1.Invasive Carcinoma of No Special Type (NST)[43]:**

* Most common type of breast cancer (~70% of all breast cancers).
* Typical presents as firm, irregular, immobile mass with skin/nipple retraction.
* Histology usually reveals malignant epithelial cells in nests/sheets with desmoplastic stroma and may show lymphovascular invasion with ER/PR+, HER2 variable and E-cadherin **positive** (vs. lobular).High-grade forms have worse prognosis.
* Treated with surgery, chemotherapy, radiation, and hormone therapy if receptor positive.

**2. Chronic Inflammation[44][45]:**

* This is a long-standing inflammation with tissue damage and repair presenting with persistent pain and palpable mass.
* Commonly associated with autoimmune diseases and infections.
* Lymphocytes, plasma cells, macrophages, and fibrosis(scar) are typical histopathological findings with risk of dysplastic transformation. It could be immunohistochemical positive for CD3 (T-cells), CD20 (B-cells), CD68 (macrophages).
* May mimic malignancy on imaging or biopsy.

**3. Fibroadenoma[44][45]**

* This is the most common benign breast tumor in women <30 of age, which presents as a well-circumscribed, mobile, painless mass ("breast mouse").
* It exhibit biphasic histological pattern (epithelial ducts and fibrous stroma) with a pericanalicular or intracanalicular growth pattern.
* It is ER/PR positive epithelium and stromal cells typically negative. This is not premalignant neoplasia but may grow with estrogen.
* Managed conservatively or excised if large or atypical.

**4. Fibrocystic Change[44][45]**

* This is a common benign neoplastic and hormonal sensitivity breast lesion that is often bilateral and cyclical lumpy-bumpy and tender breasts.
* Histological findings are spectrum of cysts, apocrine metaplasia, stromal fibrosis, ± epithelial hyperplasia and atypia that may increase cancer risk. Categorized into non-proliferative, proliferative, or atypical.
* Calcifications may be seen on mammography that could mimic malignancy.
* Managed with reassurance or biopsy if suspicious of malignant progression.

**5. Phyllodes Tumor[44][45]**

* Biphasic fibroepithelial neoplasm with leaf-like epithelial pattern and stromal proliferation. Most commonly in the breast but has been rarely reported to develop in ectopic breast tissue.
* Presents as a firm asymptomatic mobile breast mass, rarely causes bloody nipple discharge. Rarely malignant with loss of epithelial interaction in stromal components believed to lead to malignant transformation which can metastasize hematogenously.
* Histology- leaf like epithelial pattern formed by an exaggerated intracanalicular pattern. Presence of sub epithelial condensation with increased stromal cellularity adjacent to the epithelium. ER/PR positivity in the epithelium ,CD34 positive and Ki-67 increases with malignancy. Grouped into benign, borderline, and malignant, based on stromal atypia, cellularity, overgrowth, and mitotic count.
* Wide excision is the treatment of choice (not lumpectomy).

**6. Comedo-type DCIS (Comedo Carcinoma In-Situ)[44][45][46]**

* High-grade form of ductal carcinoma in situ with higher risk of progression to invasive carcinoma. Have a toothpaste discharge from the nipple.
* Presents with microcalcifications due to necrosis on mammography.
* Histological findings are typically ducts filled with pleomorphic cells and central necrosis. Characterized by prominent apoptotic cells.HER2 positivity is common, ER/PR variable and high Ki-67 index.
* Treated with surgery ± radiation, hormone therapy if ER positive.

**7. Ductal Ectasia[45]**

* Dilated ducts near the nipple, often seen in perimenopausal women. Presents with nipple retraction, discharge (green/brown), and possible pain or mass. Inflammation can be the cause of nipple retraction. Often benign but mimics carcinoma clinically.
* Histological findings are dilated ducts, lipid-laden macrophages and periductal fibrosis.
* No specific immunostains but they may show CD68 positive macrophages.
* Managed conservatively or with excision if symptomatic.

**8. Lymphoma (Primary or Secondary Breast)[46][47]**

* Rare in breast; most are **B-cell** lymphomas often mistaken for carcinoma. Typically presents as painless, rapidly growing mass and could be systemic.
* Histology shows sheets of atypical lymphoid cells replacing normal tissue immunostains for CD20+, CD3– (B-cell) and possible high Ki-67 proliferation index .
* Treatment is primarily with chemotherapy , while surgery is less likely.
* Prognosis depends on subtype and stage.

**9. Lymphoepithelioma-like Carcinoma (LELC)[48][49]**

* Rare breast carcinoma that resembles nasopharyngeal carcinoma. Presents as a firm breast mass; often mistaken for lymphoma.
* Histology shows syncytial sheets of malignant cells with dense lymphoid stroma.
* Immunostains for cytokeratin+ve , EMA+ve and often triple-negative (ER/PR/HER2–).May show PD-L1 positivity (immunotherapy potential). EBV+ve is only seen in nasopharyngeal carcinoma (Absent in the breast).
* Better prognosis than other high-grade tumors.

**10. Melanoma[50][51]**

* Aggressive skin cancer from melanocytes may metastasize to breast, characterized by asymmetrical pigmented lesion with irregular borders and colors. May mimic Paget’s disease if on nipple.
* Histology is made up of atypical melanocytes with pagetoid spread with typical biomarkers like S100+, HMB-45+, Melan-A+, and SOX10+.
* Sentinel lymph node biopsy is important in staging.
* Treated with wide excision ± immunotherapy.

**11. Intraductal Papilloma[45][51][52]**

* Benign epithelial tumor within lactiferous ducts and a common cause of bloody or serous nipple discharge. Solitary forms are central and multiple ones are peripheral, with malignant tendencies.
* Histology is typified by fibrovascular cores lined by double-layered epithelium and immunostaining for p63+, SMA+ (myoepithelium); CK5/6+ and ER+ (luminal).
* Low malignant potential but needs histological exam.
* Excision is often done because it may harbor atypia or DCIS.

**12. Metastatic Breast Cancer[51][53][54]**

* Breast cancer can spread to distant organs such as bone, liver, brain, and lungs. The clinical manifestations is dependent on metastatic sites.
* Histology is similar to primary tumor and glandular features common.
* Immunostaining may be positive for CK7, GCDFP-15, and mammaglobin(to confirm breast origin).HER2, ER/PR status may differ from primary.
* Incurable but treatable. The goal is palliation because this is a common cause of death among breast cancers.

## **MANAGEMENTS**

The management breast cancer is a multidisciplinary approach tailored to individual patient's needs. In general, heart disease and malignancy remain the most common cause of mortality in the last two decades necessitating aggressive management ,and thus the available options for breast cancers usually include the following [6] **[55]**[56][57][58]:

* Surgery: breast-conserving surgery (lumpectomy) or mastectomy, depending on the tumor characteristics and patient preferences.
* Lymph Node Evaluation: Sentinel and axillary lymph node biopsy and dissection.
* Radiation Therapy: Recommended following surgery to reduce the risk of recurrence.
* Chemotherapy: Systemic chemotherapy is often used in the treatment of MBC, considering its high-grade nature and triple-negative phenotype.
* Hormone Therapy: This is often less like applicable to Medullary breast carcinomas due to lack of hormone receptor expression.

Medullary breast carcinoma has a more favorable prognosis compared to other subtypes of breast cancer[56][58]. However, the prognosis may vary depending on the characteristics and stage of the tumor at the time of diagnosis and individual health status. The management of MBC may include[56][57][58][59]:

* **Ongoing surveillance and routine follow-up visits** are essential for early detection of recurrence or metastasis.
* **Genetic counseling and testing** may be beneficial for individuals with medullary breast carcinoma (MBC), especially due to its association with hereditary mutations like **BRCA1**.
* **Psychosocial support**, including emotional counseling and involvement in support groups, offers vital assistance to patients and their families throughout the course of diagnosis, treatment, and recovery.

Medullary breast carcinoma (MBC) is currently managed similarly to invasive ductal carcinoma (IDC), typically through breast-conserving surgery or mastectomy, followed by adjuvant therapy such as chemotherapy or radiotherapy[12][57][58][59]. Due to the frequent absence of estrogen and HER2 receptors, chemotherapy remains the primary systemic option, though its benefit is debated in the literature [19][28][59].

Treatment strategies do not differ significantly between typical and atypical subtypes of MBC; the classification holds prognostic rather than therapeutic significance[6][58]. Management may involve modified or radical mastectomy in combination with radiation or chemotherapy, depending on tumor stage. MBC is generally responsive to both radiation and chemotherapy[18][60].

For tumors measuring 3 cm or less, breast-conserving surgery with adjuvant radiation is often appropriate. Chemotherapy is typically indicated in cases of larger tumors, lymph node involvement, or lymphovascular invasion[58][59][60].

**DISCUSSION**

In 2019, the World Health Organization (WHO) Blue Book, which continuously provides updated indispensable international standards for the classification of breast tumors globally, reported that 25% of all invasive breast cancers (BCs) are of the special subtype [1]. Medullary Breast Carcinoma (MBC) comprises 3–5% of these special subtypes (1–7% of all breast cancers) and has a better prognosis when compared with invasive ductal carcinoma (IDC)[6][55][57][58]. This has been demonstrated even after correcting confounding factors, with MBC showing superior overall survival (OS) and cancer-specific survival (CSS) compared to IDC [3][16][17]. Several factors are considered prognostic indicators to determine cancer overall survival in terms of the 10-year survival rate. These include tumor size, lymph node status, the Nottingham grade, and mitotic counts per mm² [9]. A large cohort study of 3,348 patients with MBC conducted by Martinez et al. identified patient and tumor-specific factors influencing survival[21]. They reported that aside from common prognostic factors shared with IDC, including tumor size, number of lymph node metastases (LNM) and presence or absence of lymph node metastasis. The distinct features highly predictive for MBC include lymph node status, race, age, and progesterone receptor (PR) status [26, 28, 29]. Ridolfi et al. previously noted that tumor sizes <3 cm had a survival rate of 92%, which was confirmed by Martinez et al.’s finding that tumors <22 mm and >22 mm showed 83% and 73% survival rates, respectively [8][21][26][30][31]. Moreover, the syncytial growth pattern, stipulated by Ridolfi et al. to be greater than 75% as one of the diagnostic criteria, also doubles as a predictor of survival. High survival rates are seen in patients with 75–95% syncytial growth, with moderate and significantly lower survival observed in patients with less than 75% and 50% syncytial growth, respectively [8][21][22]. On one end of the spectrum, understanding these prognostic factors helps avoid aggressive treatment in patients with favorable outcomes. On the other hand, it allows identification of patients with predicted poor outcomes or possible recurrence, enabling prompt and aggressive therapy. Compared to common breast malignancies, MBC generally has a better prognosis, with 5-year survival rates ranging from 82% to 84%, compared to 50% to 63% for IDC NOS [12][15][21][24]. Previously, lymph node status, age, tumor size, grade, and hormone receptor status (ER, PR, HER2) were considered significant prognostic factors. Recently, increasing age at diagnosis has also been considered a factor. Good prognosis is associated with non–triple-negative status, less inflammatory changes, and tumor-infiltrating lymphocytes, although these do not alter therapy [10][27][59[60].

**CONCLUSION**

Medullary breast carcinoma (MBC) represents an intriguing paradox in oncology. Despite its aggressive microscopic appearance, it often follows a comparatively favorable clinical course. Although it is less extensively researched than other breast‑cancer subtypes, ongoing studies are beginning to reveal the biological factors that make MBC distinctive. Appreciating these nuances is vital, not merely for classification, but for personalizing therapy. As research into tumor genetics and immuno‑oncology advances, it promises to refine diagnosis and expand treatment options for this uncommon yet clinically significant malignancy.

**REFERENCES**

1. Smolarz B, Zadrożna Nowak A, Romanowicz H. Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). Cancers (Basel) [Internet]. 2022 May 1 [cited 2025 Jan 24];14(10):2569. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9139759/>
2. Song B, Singh H. Rare Breast Cancers Review. Healthcare 2024, Vol 12, Page 2483 [Internet]. 2024 Dec 9 [cited 2025 Jan 28];12(23):2483. Available from: <https://www.mdpi.com/2227-9032/12/23/2483/htm>
3. Rakha EA, Tse GM, Quinn CM. An update on the pathological classification of breast cancer. Histopathology. 2023 Jan 1;82(1):5–16.
4. Reinfuss, M et al. “Typical medullary carcinoma of the breast: a clinical and pathological analysis of 52 cases.” *Journal of surgical oncology* vol. 60,2 (1995): 89-94. doi:10.1002/jso.2930600205
5. Chen Y, Xu Z, Chen Y, Dai Y, Ding J. Comparison of the prognosis of medullary breast carcinoma and invasive ductal carcinoma: a SEER-based study. Transl Cancer Res [Internet]. 2024 Jan 31 [cited 2025 Jan 24];13(1):231–48. Available from: <https://tcr.amegroups.org/article/view/82460/html>
6. Kleer CG. Carcinoma of the breast with medullary-like features: diagnostic challenges and relationship with BRCA1 and EZH2 functions. Arch Pathol Lab Med [Internet]. 2009 Nov [cited 2025 Jan 24];133(11):1822–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/19886718/>
7. Bertucci F, Finetti P, Cervera N, et al. Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. Cancer Res. 2006;66(9):4636–4644.
8. Ridolfi RL, Rosen PP, Port A, Kinne D, Mike V. Medullary carcinoma of the breast: a clinicopathologic study with 10-year follow-up. Cancer. 1977;40(4):1365–1385.
9. Tse GM, Tan PH, Putti TC. Histological and immunohistochemical criteria in the diagnosis of medullary carcinoma of the breast. J Clin Pathol. 2004;57(3):250–255.
10. Bogdanova N, Helbig S, Dörk T. Hereditary breast cancer: ever more pieces to the polygenic puzzle. Hered Cancer Clin Pract. 2013;11(1):12.
11. Beal SH, Martinez SR, Canter RJ, Chen SL, Khatri VP, Bold RJ. Survival in 12,653 breast cancer patients with extensive axillary lymph node metastasis in the anthracycline era. Med Oncol. 2011;28(3):738-44.
12. Vincent-Salomon A, Gruel N, Lucchesi C, MacGrogan G, Dendale R, Sigal-Zafrani B, Longy M, Raynal V, Pierron G, de Mascarel I, Taris C, Stoppa-Lyonnet D, Pierga JY, Salmon R, Sastre-Garau X, Fourquet A, Delattre O, de Cremoux P, Aurias A. Identification of typical medullary breast carcinoma as a genomic sub-group of basal-like carcinomas, a heterogeneous new molecular entity. Breast Cancer Res. 2007;9(2):R24. doi: 10.1186/bcr1666. PMID: 17417968; PMCID: PMC1868916.
13. Tusher VG, Tibshirani R, Chu G. Significance analysis of microarrays applied to the ionizing radiation response. Proc Natl Acad Sci U S A. 2001 Apr 24;98(9):5116-21. doi: 10.1073/pnas.091062498. Epub 2001 Apr 17. Erratum in: Proc Natl Acad Sci U S A 2001 Aug 28;98(18):10515. PMID: 11309499; PMCID: PMC33173.
14. Rakha EA, Ellis IO. Triple-negative/basal-like breast cancer: review and update. Histopathology. 2009;55(6):589–602.
15. Diaz NM, Sneige N, Krishnamurthy S, Middleton LP, Laucirica R, Resetkova E, et al. Medullary carcinoma of the breast: a clinicopathologic study of 44 cases with emphasis on the diagnostic criteria. Hum Pathol. 2003;34(2):144-50.
16. Chu Z, Lin H, Liang X, Huang R, Zhan Q, Jiang J, et al. Clinicopathologic characteristics of typical medullary breast carcinoma: a retrospective study of 117 cases. PLoS One. 2014;9(10):e109955.
17. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA. 2003;100:8418–8423. doi: 10.1073/pnas.0932692100. [[DOI](https://doi.org/10.1073/pnas.0932692100)] [[PMC free article](https://pmc.ncbi.nlm.nih.gov/articles/PMC166244/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/12829800/)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Proc%20Natl%20Acad%20Sci%20USA&title=Repeated%20observation%20of%20breast%20tumor%20subtypes%20in%20independent%20gene%20expression%20data%20sets&author=T%20Sorlie&author=R%20Tibshirani&author=J%20Parker&author=T%20Hastie&author=JS%20Marron&volume=100&publication_year=2003&pages=8418-8423&pmid=12829800&doi=10.1073/pnas.0932692100&)]
18. Aulmann S, Adler N, Rom J, Helmchen B, Schirmacher P, Sinn HP. c-myc amplifications in primary breast carcinomas and their local recurrences. J Clin Pathol. 2006 Apr;59(4):424-8. doi: 10.1136/jcp.2005.029264. Epub 2006 Feb 23. PMID: 16497871; PMCID: PMC1860364.
19. Tsuda H, Tani Y, Weisenberger J, Kitada S, Hasegawa T, Murata T, Tamai S, Hirohashi S, Matsubara O, Natori T. Frequent KIT and epidermal growth factor receptor overexpressions in undifferentiated-type breast carcinomas with 'stem-cell-like' features. Cancer Sci. 2005 Jun;96(6):333-9. doi: 10.1111/j.1349-7006.2005.00060.x. PMID: 15958055; PMCID: PMC11159312.
20. Van de Rijn M, Perou CM, Tibshirani R, Haas P, Kallioniemi O, Kononen J, Torhorst J, Sauter G, Zuber M, Köchli OR, Mross F, Dieterich H, Seitz R, Ross D, Botstein D, Brown P. Expression of cytokeratins 17 and 5 identifies a group of breast carcinomas with poor clinical outcome. I am J Pathol. 2002 Dec;161(6):1991-6. doi: 10.1016/S0002-9440(10)64476-8. Erratum in: Am J Pathol. 2003 Jul;163(1):377. PMID: 12466114; PMCID: PMC1850928.
21. Martinez SR, Beal SH, Canter RJ, Chen SL, Khatri VP, Bold RJ. Medullary carcinoma of the breast: a population-based perspective. Med Oncol. 2011 Sep;28(3):738-44. doi: 10.1007/s12032-010-9526-z. PMID: 20390465; PMCID: PMC4596814.
22. Beal SH, Martinez SR, Canter RJ, Chen SL, Khatri VP, Bold RJ. Survival in 12,653 breast cancer patients with extensive axillary lymph node metastasis in the anthracycline era. Med Oncol. doi: 10.1007/s12032-009-9396-4.
23. Gaffey MJ, Mills SE, Frierson HF, Jr, Zarbo RJ, Boyd JC, Simpson JF, Weiss LM. Medullary carcinoma of the breast: interobserver variability in histopathologic diagnosis. Mod Pathol. 1995;8(1):31–38 [[PubMed](https://pubmed.ncbi.nlm.nih.gov/7731939/)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mod%20Pathol&title=Medullary%20carcinoma%20of%20the%20breast:%20interobserver%20variability%20in%20histopathologic%20diagnosis&author=MJ%20Gaffey&author=SE%20Mills&author=HF%20Frierson&author=RJ%20Zarbo&author=JC%20Boyd&volume=8&issue=1&publication_year=1995&pages=31-38&pmid=7731939&) .
24. Jeong S, Lim H, Lee J, Park M, Yoon J han, Park JG, et al. Medullary carcinoma of the breast: MRI findings. AJR Am J Roentgenol. 2012.
25. Dutta S, Banerjee S, Bera A, Mandal S, Banerjee C. MEDULLARY CARCINOMA OF THE BREAST-EPIDEMIOLOGY, THE PATTERN OF CARE, AND TREATMENT OUTCOME: EXPERIENCE FROM THE TERTIARY CANCER CARE CENTER. Asian Journal of Pharmaceutical and Clinical Research. 2022.
26. Cao AY, He M, Huang L, Shao ZM, Di G. Clinicopathologic characteristics at diagnosis and the survival of patients with medullary breast carcinoma in China: a comparison with infiltrating ductal carcinoma-not otherwise specified. World J Surg Oncol. 2013.
27. Romaniuk P, Romaniuk I, Postupolski M. Medullary breast cancer: A concise review of epidemiology, genetics, diagnostics and treatment. Oncol Lett. 2016;12(6):4495-4498.
28. Yedjou CG, Sims JN, Miele L, Noubissi F, Lowe L, Fonseca DD, Alo RA, Payton M, Tchounwou PB. Health and Racial Disparity in Breast Cancer. Adv Exp Med Biol. 2019;1152:31-49. doi: 10.1007/978-3-030-20301-6\_3. PMID: 31456178; PMCID: PMC6941147.
29. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lønning PE, Børresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001 Sep 11;98(19):10869-74. doi: 10.1073/pnas.191367098. PMID: 11553815; PMCID: PMC58566.
30. Foote FW, Stewart FW. Lobular carcinoma in situ: A rare form of mammary cancer. Am J Pathol. 1941 Jul;17(4):491-496.3. doi: 10.3322/canjclin.32.4.234. PMID: 19970575; PMCID: PMC1965212.
31. Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, Joensuu H, Dieci MV, Badve S, Demaria S, Gray R, Munzone E, Lemonnier J, Sotiriou C, Piccart MJ, Kellokumpu-Lehtinen PL, Vingiani A, Gray K, Andre F, Denkert C, Salgado R, Michiels S. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers. J Clin Oncol. 2019 Mar 1;37(7):559-569. doi: 10.1200/JCO.18.01010. Epub 2019 Jan 16. PMID: 30650045; PMCID: PMC7010425.
32. Kővári B, Ormándi K, Simonka Z, Vörös A, Cserni G. Apocrine Encapsulated Papillary Carcinoma of the Breast: The First Reported Case with an Infiltrative Component. J Breast Cancer. 2018 Jun;21(2):227-230. doi: 10.4048/jbc.2018.21.2.227. Epub 2018 Jun 20. PMID: 29963120; PMCID: PMC6015972.
33. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014 Nov;15(12):1303-10. doi: 10.1016/S1470-2045(14)70460-7. Epub 2014 Oct 15. PMID: 25439688; PMCID: PMC4291166.
34. Li CI. Risk of mortality by histologic type of breast cancer in the United States. Horm Cancer. 2010 Jun;1(3):156-65. doi: 10.1007/s12672-010-0016-8. PMID: 21761358; PMCID: PMC10357995.
35. Park I, Kim J, Kim M, Bae SY, Lee SK, Kil WH, Lee JE, Nam SJ. Comparison of the characteristics of medullary breast carcinoma and invasive ductal carcinoma. J Breast Cancer. 2013 Dec;16(4):417-25. doi: 10.4048/jbc.2013.16.4.417. Epub 2013 Dec 31. PMID: 24454464; PMCID: PMC3893344.
36. Foekens JA, Look MP, Bolt-de Vries J, Meijer-van Gelder ME, van Putten WL, Klijn JG. Cathepsin-D in primary breast cancer: prognostic evaluation involving 2810 patients. Br J Cancer. 1999 Jan;79(2):300-7. doi: 10.1038/sj.bjc.6690048. PMID: 9888472; PMCID: PMC2362199.
37. Howat JM, Barnes DM, Harris M, Swindell R. The association of cytosol oestrogen and progesterone receptors with histological features of breast cancer and early recurrence of disease. Br J Cancer. 1983 May;47(5):629-40. doi: 10.1038/bjc.1983.101. PMID: 6849801; PMCID: PMC2011376.
38. Alfaro A, Catelain C, El-Masri H, Rameau P, Lacroix-Triki M, Scoazec JY, et al. Characterization and spatial distribution of infiltrating lymphocytes in medullary, and lymphocyte-predominant triple negative breast cancers. NPJ Breast Cancer. 2024 Dec 1;10(1).
39. Chandrika, Permi HS, Prasad HLK, Mohan R, Shetty KJ, Patil C. Synchronous bilateral medullary carcinoma of breast: Is it metastasis or second primary? J Cancer Res Ther. 2012.
40. Bloom HJG, Richardson WW, Field JR. Host resistance and survival in carcinoma of breast: a study of 104 cases of medullary carcinoma in a series of 1, 411 cases of breast cancer followed for 20 years. Br Med J. 1970;3(5716):181–188.
41. Ridolfi RL, Rosen PP, Port A, Kinne D, Mikj~ V. MEDULLARY CARCINOMA OF THE BREAST A Clinicopathologic Study with 10 Year Follow-Up. MEDULLARY CARCINOMA IS AN [Internet]. 1977 [cited 2025 Jan 24];40:1365–85. Available from: <https://onlinelibrary.wiley.com/terms-and-conditions>
42. Moore OS, Foote FW. THE RELATIVELY FAVORABLE PROGNOSIS OF MEDULLARY CARCINOMA OF THE BREAST. Cancer. 1949;2(5):635–642.
43. Vinay Kumar, Abbas, A.K., Fausto, N. and Mitchell, R. (2012). *Robbins Basic Pathology.* London: Elsevier Health Sciences.
44. Tan, Puay Hoon et al. “The 2019 World Health Organization classification of tumours of the breast.” *Histopathology* vol. 77,2 (2020): 181-185. doi:10.1111/his.14091
45. Rosen, P.P. and Syed (2015). *Breast Pathology*. Lippincott Williams & Wilkins.
46. Shekhar MP, Tait L, Pauley RJ, Wu GS, Santner SJ, Nangia-Makker P, Shekhar V, Nassar H, Visscher DW, Heppner GH, Miller FR. Comedo-ductal carcinoma in situ: A paradoxical role for programmed cell death. Cancer Biol Ther. 2008 Nov;7(11):1774-82. doi: 10.4161/cbt.7.11.6781. Epub 2008 Nov 12. PMID: 18787417; PMCID: PMC4657570.
47. Swerdlow, S.H. (2017). *WHO classification of tumours of haematopoietic and lymphoid tissues*. [online] Lyon: International Agency for Research on Cancer. Available at: <http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017> [Accessed 30 Apr. 2019].
48. Who Classification of Tumours Editorial Board, International Agency for Research on Cancer and World Health Organization (2019). *WHO classification of tumours. Breast Tumours*. Lyon: International Agency for Research on Cancer.
49. O’Connor, O.A., Won Seog Kim and Zinzani, P.L. (2021). *The Peripheral T-Cell Lymphomas*. John Wiley & Sons.
50. Rigel, D.S., Burshtein, J., Shah, M. and Zakria, D. (2025). *Melanoma and Pigmented Lesion Update, An Issue of Dermatologic Clinics*. Elsevier Health Sciences.
51. McCart Reed, A.E., Kalaw, E.M. and Lakhani, S.R. (2021). An Update on the Molecular Pathology of Metaplastic Breast Cancer. *Breast Cancer: Targets and Therapy*, Volume 13, pp.161–170. doi:<https://doi.org/10.2147/bctt.s296784>.
52. Ajisaka H, Tsugawa K, Noguch M, Miwa M, Nonomura A. Histological subtypes of ductal carcinoma in situ of the breast. Breast Cancer. 2002;9(1):55-61. doi: 10.1007/BF02967548. PMID: 12196723.
53. Miettinen, M. (2010). *Modern Soft Tissue Pathology*. Cambridge University Press.
54. Ouissam Al Jarroudi (n.d.). *Breast Cancer Research and Treatment*. Springer Nature.
55. Adedeji Okikiade, Chidinma Kanu , Oluwadamilare Iyapo , Ololade Omitogun , and Richard Adetoye . 2024. “Comparative Analysis of Mortality in the United States in 1980 and 2019”. *Archives of Current Research International* 24 (9):276-92. https://doi.org/10.9734/acri/2024/v24i9893
56. Limaiem F, Mlika M. Medullary Breast Carcinoma. [Updated 2023 Jan 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK542292/>
57. Eichhorn JH. Medullary carcinoma, provocative now as then. Semin Diagn Pathol. 2004 Feb;21(1):65-73. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/15074561)]
58. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, Rock CL, Kealey S, Al-Delaimy WK, Bardwell WA, Carlson RW, Emond JA, Faerber S, Gold EB, Hajek RA, Hollenbach K, Jones LA, Karanja N, Madlensky L, Marshall J, Newman VA, Ritenbaugh C, Thomson CA, Wasserman L, Stefanick ML. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007 Jul 18;298(3):289-98. doi: 10.1001/jama.298.3.289. PMID: 17635889; PMCID: PMC2083253.
59. Wang J, Wu SG. Breast Cancer: An Overview of Current Therapeutic Strategies, Challenge, and Perspectives. Breast Cancer (Dove Med Press). 2023 Oct 20;15:721-730. doi: 10.2147/BCTT.S432526. PMID: 37881514; PMCID: PMC10596062.
60. Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. CA Cancer J Clin. 2014 May-Jun;64(3):186-94. doi: 10.3322/caac.21225. Epub 2014 Mar 19. PMID: 24647877.