HHS Public Access

Author manuscript

Curr Oncol Rep. Author manuscript; available in PMC 2022 March 23.

Published in final edited form as:

Curr Oncol Rep. ; 23(5): 54. doi:10.1007/s11912-021-01048-4.

Rare Breast Cancer Subtypes

Sarah Jenkins, M.D., Ph.D.[#1,2], **Megan E. Kachur, M.D.**[#3], **Kamil Rechache, M.D.**[#1,2], **Justin M. Wells, M.D.**[3,4], **Stanley Lipkowitz, M.D., Ph.D.**[1,4]

[1]Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892

[2]Medical Oncology Service, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892

[3]Pathology Department, Walter Reed National Military Medical Center, Bethesda MD 20889

[#] These authors contributed equally to this work.

Abstract

Purpose of Review.—Breast cancer is a collection of diseases including the more common invasive ductal and lobular carcinomas and rarer subtypes of breast cancer. This review summarizes the features of rare breast cancers.

Recent Findings.—Each of the rare tumors have defined pathological and clinical features that impact treatment recommendations. In this review, we summarize these for each rare type of breast cancer and where available we include molecular features of each tumor.

Summary.—Rare subtypes of breast cancer each have unique features. In many cases, data is limited for the optimal treatment approaches.

Keywords

Breast Cancer; Rare Breast Cancer Subtypes

Introduction

Breast cancer is collection of diseases defined by distinct pathological (*e.g.,* ductal, lobular, mucinous, etc.) and molecular characteristics (*e.g.,* estrogen receptor (ER) and progesterone receptor expression (PR), HER2 amplification, and more recently transcriptome based classifications such as luminal and basal cancers) [1–3]. The World Health Organization (WHO) has classified breast cancer based on histological features into WHO classifications

[4]Corresponding Authors Stanley Lipkowitz, lipkowis@navmed.nci.nih.gov, Justin Wells, justin.m.wells8.civ@mail.mil.

Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, National Cancer Institute, or U.S. Government.

of breast cancer [4]. The majority of breast cancers are classified as invasive ductal carcinoma of no special type (IDC) (75–80%) or invasive lobular carcinonma, classical type (ILC) (10–15%). This review will focus on the rare breast cancer subtypes that make up the rest of breast cancer diagnoses organized by the prognosis of the rare tumor (Table 1). These rare subtypes each have distinct pathological and clinical features that impact the prognosis and treatment of these breast cancer subtypes. Due to the space limitations of this review, benign breast tumors, mesenchymal tumors such as breast sarcomas, and fibroepithelial tumors such as phyllodes tumors will not be discussed.

Rare breast cancer with good prognosis (ER and PR positive)

Mucinous Carcinoma—Mucinous carcinoma of the breast accounts for approximately 2–3% of all primary breast cancer diagnoses [4]. It is characterized by clusters and sheets of malignant cells floating in extracellular mucin and separated by fibrous septae. The percentage of mucin content can be used to further divide mucinous carcinomas into pure (>90%) and mixed (10–90%) subgroups. It has exclusively low-grade cytology; tumors with high-grade cytology are considered IDC with mucin production. Signet ring cell differentiation is not synonymous with this entity and may be seen in ILC, IDC, and metastasis from other organs. It is associated with a high frequency of ER and PR expression and lack of HER2 amplification (HER2-) [5]. Unlike colorectal mucinous adenocarcinoma, mucinous carcinoma of breast has a low level of genetic instability and lacks any distinct molecular abnormalities [4].

Mucinous carcinomas of breast tend to present in the post-menopausal setting, with a median age of 71 years [5]. These tumors are further characterized by a smaller size and decreased lymph node involvement at presentation when compared to IDC. As the above defining characteristics suggest, mucinous carcinoma of breast is associated with a favorable prognosis. In a large population of patients with mucinous adenocarcinoma of breast (n=11,422), only two percent of patients had distant metastases at time of surgical intervention; most patients presented with locoregional disease [5]. When compared to IDCs, mucinous carcinomas of the breast showed improved breast cancer specific survival at 10- (94% vs 89%), 15- (85% vs 72%), and 20-years (81% vs 62%) [5]. An additional study by Marrazzo *et al.* showed a 5-year overall survival of 92.1% [6]. This indolent course was illustrated in a case report of a 77-year-old woman [7]. She initially presented with a 4 cm tumor and was recommended surgical treatment. The patient refused treatment and was next seen three years later. Her tumor had ulcerated and grown to a maximum diameter of 13 cm but did not have any locoregional or distant metastatic disease. She was subsequently treated with a mastectomy and axillary lymph node dissection and adjuvant anastrozole without recurrence.

Due to its favorable clinical course, mucinous carcinoma of breast is treated with surgical removal by breast conserving surgery or mastectomy with sentinel node biopsy, often followed by adjuvant endocrine therapy. These recommendations are largely based on the strong ER/PR positivity observed in mucinous breast carcinomas and case studies. A retrospective study of women with mucinous carcinoma of the breast (n=268) showed adjuvant hormonal therapy to be associated with an improved disease-free survival and

overall survival in multivariate analysis [8]. Chemotherapy is not generally recommended. A large-scale retrospective study from the Korean Breast Cancer Registry found adjuvant chemotherapy did not significantly improve prognosis in most cases of mucinous carcinoma, showing benefit only in the N3 stage setting [9]. To our knowledge, this question of de-escalation of therapy has not been addressed in a prospective manner.

Tubular Carcinoma—Pure tubular carcinoma accounts for 1–2% of all diagnosed invasive breast carcinomas [10]. Histology is characterized by >90% tubules with a single layer of neoplastic epithelium and open lumina. Myoepithelial cells are absent. This histology is strongly associated with co-occurrence of columnar cell change, flat epithelial atypia, and low-grade *in situ* carcinomas in the so-called Rosen's triad. Cytologic features are typically grade one and the histologic grade is invariably one. Nearly all tubular carcinomas have strong and diffuse expression of the ER and PR and lack HER2 amplification [4]. Departures from this expression pattern should be re-reviewed for pathology to ensure accuracy of diagnosis. Chromosomal alterations characteristic of tubular carcinoma includes: loss of 16q, 8p, and 3p as well as gain of 1q, 16p, and 11q (ATM gene) [11]. Most often, pure tubular carcinomas are low-grade, well-differentiated cancers that genetically cluster into the luminal A expression pattern [11].

There are no unique aspects of clinical presentation. These cancers typically occur in post-menopausal women and have a low incidence of locoregional and distant metastasis [12]. In a retrospective review, Javid *et al.* found a <1% incidence of local breast cancer recurrence in a cohort of tubular carcinoma patients (n=111) [13]. No patient in this cohort developed regional or distant metastasis during a 72-month follow-up period. As such, tubular carcinomas are regarded as having a favorable prognosis. A larger scale retrospective study from the SEER database estimated a 10-year breast cancer specific survival of 98.1% and a 10-year overall survival of 82% [14]. Even when compared against low-grade IDC, tubular carcinomas were noted to have superior survival [15].

Due to the favorable prognosis associated with this histology, less aggressive clinical care is typically recommended, with judicious use of adjuvant therapy that is based on primary tumor size and regional lymph node status [10]. Treatment modalities are similar to that for IDC but recommendations include omitting use of adjuvant chemotherapy for node negative tumors and to consider omitting use of adjuvant endocrine therapy in node negative tumors that are <3 cm. Adjuvant endocrine therapy is recommended for tumors ≥3cm or those that are node positive. The addition of adjuvant chemotherapy to endocrine therapy can be considered in patients with lymph node positive disease of any size [10].

Cribriform Carcinoma—Invasive cribriform carcinoma (ICC) of the breast was first described in detail as a type of ductal carcinoma of the breast by Page *et al.* in 1983 [16]. The overall prevalence is a rare, representing 0.4% of breast cancers and is generally associated with a good prognosis [4, 16]. Histologically, greater than 90% of the tumor must be composed of bland epithelial cells forming dense well-demarcated rounded islands with central "punched out" areas with an absence of epithelial cells. This is reminiscent of the cribriform type of ductal carcinoma *in situ* (DCIS), with a notable absence of myoepithelial cells surrounding the epithelial cells, and desmoplastic stromal response in excess of that

seen in an in-situ lesion. These cases are often associated with an *in situ* component which can make the identification of invasion diagnostically challenging. Overall, cribriform carcinoma of the breast is usually ER+, PR+ and HER2− [4]v. According to a 2013 study by Zhang *et al.* which evaluated 51 patients, 72.5% of cases showed proliferation index (Ki67) ≤ 14%.

The median age at diagnosis is 54–63 years [17]. Liu *et al.*, using the SEER database to analyze the clinicopathological characteristics of cribriform carcinoma, showed that this special histologic type exhibits a lower grade, smaller tumor size, lesser lymph nodes involvement, earlier stage, higher positivity rate of hormone expression, and a lower HER2 amplification rate than IDC [17]. In addition, several other previous studies have shown that the rate of axillary lymph node metastasis is 15.9%−25.5% and lower than that of IDC [17–19]. Interestingly, cribriform carcinoma seems to generally have a very favorable prognosis irrespective of status of lymph node metastases.

Currently, treatment of ICC is based on evidence from IDC. Review of SEER database showed that lumpectomy rates were higher in patients with ICC compared to IDC (67.9% vs. 60.4%, $P < 0.001$) [17]. Adjuvant radiation, however, is used with similar frequency in patients with ICC or IDC [17]. In a 2015 study by Munzone *et al.* which investigated the outcomes of postmenopausal women with hormone receptor-positive (HR+), early invasive breast cancer with special tumor histotypes (mucinous, tubular, or cribriform) who were enrolled in the monotherapy cohort of the BIG 1–98 trial, women with tubular or cribriform tumors showed the best outcomes compared with those in the other three histologic groups [20]. Women with tubular or cribriform carcinoma had better disease recurrence free interval (DRFI; 5-year DRFI: 97.8%, 98.8%, respectively) than those with IDC (90.9%) or other (92.1%) carcinomas [20]. Several other studies have also shown that the prognosis of ICC is better than that of IDC with a 10-year survival rate of 90% to 100% [16–19, 21]. For these reasons, there are recommendations that this favorable histological subtype of tumor may be suitable for no adjuvant therapy or just endocrine therapy alone [22].

However, utilizing the SEER database, Liu *et al.* found that when using multivariate cox analysis for potential confounders, there was no survival advantage in ICC compared with IDC [17]. Furthermore, after matching ICC with IDC by age, tumor stage, tumor grade, ER status, and PR status, ICC showed nearly the same outcomes as IDC [17]. These results imply that the ICC histological type is not an independent prognostic factor. Moreover, results from subgroup analyses showed that the prognostic superiority of ICC was not exhibited in tumor grade subgroups, indicating that the different survival outcomes may primarily be as a result from the distribution of tumor grade in these two tumor types [17].

Invasive Papillary Carcinoma—Papillary cancers of breast are rare, accounting for approximately 0.5% of all diagnosed breast cancers. These cancers can be subdivided into several histologically distinct subdivisions, including encapsulated papillary carcinoma, solid papillary carcinoma, and invasive papillary carcinoma [4]. The first two are most often treated like *in situ* processes and are not discussed in depth here. Invasive papillary breast cancer consists of dilated ducts and cysts containing papillary structures with fibrovascular cores without myoepithelial cells. Histologic grading (Nottingham) is instead based on the

presence of polarized tumor cells with central lumina rather than true gland formation [4]. The classical presentation of invasive papillary breast cancer includes bloody nipple discharge in association with an abnormal breast mass that is most often located beneath the nipple. It occurs most often in post-menopausal women and has been associated with a more indolent clinical course and better prognosis than IDC.

This indolent clinical course was documented in a natural history observation over a 10-year period in a patient with invasive papillary carcinoma who refused treatment [23]. Despite the patient having a large primary tumor (10.4 × 7.2 × 3.5 cm) and axillary lymph node involvement at baseline, she remained without distant metastatic disease after 10 years without any treatment. In a large, retrospective Surveillance, Epidemiology, and End Result (SEER) database study, invasive papillary breast carcinoma was noted to present with smaller tumor sizes, lower grade tumors, and reduced incidence of lymph node involvement as compared to IDC [24]. While the five-year disease-specific survival rates were significantly better in invasive papillary breast carcinoma compared to IDC (97.5% vs 93%), this significant difference was not seen after multivariate analysis and adjustment for other prognostic factors. In a retrospective analysis from a single institute, patients with invasive papillary carcinoma (n=284) were noted to have an improved 5-year overall survival and disease-free survival as compared to invasive ductal carcinoma [25].

Invasive papillary breast carcinoma almost universally expresses ER and PR, with a higher incidence of both ER and PR positivity than IDC [24]. It is also characterized by lack of HER2 amplification and a low-to-moderate cell proliferation index. There are no disease-specific guidelines defining care in this patient population. These patients most often undergo definitive surgical management with or without adjuvant radiation. In early-stage invasive papillary breast cancer (defined as stage T1–2 N0 disease), lumpectomy followed by radiation therapy was associated with an improved overall survival when compared with lumpectomy alone or mastectomy alone [26]. Due to its indolent nature, there is no clear role for the routine use of endocrine therapy or adjuvant chemotherapy. However, a recent case report details the case of a patient with invasive papillary breast carcinoma who initially deferred definitive surgical excision in favor of neoadjuvant endocrine therapy [27]. In this case, 12 months of treatment with neoadjuvant letrozole at 2.5 mg po daily was sufficient to produce a pathological complete response at subsequent surgical excision.

Rare breast cancer with good prognosis (ER and PR negative or low)

Medullary Carcinoma—Medullary breast carcinoma (MedBC) is a rare morphologic subtype of IDC accounting for approximately 3–5% of cases. Microscopically, medullary pattern is a well-circumscribed lesion with a “pushing border” pattern of expansion rather than infiltrative features, high-grade cytologic characteristics, a syncytial or sheet-like arrangement of cells, and a characteristic accompanying dense lymphocytic infiltrate. The majority of MedBCs are histologically triple negative breast cancers (TNBC) lacking ER and PR expression and HER2 amplification often with cytokeratin 5/6 positivity [28, 29]. The prevalence of medullary pattern among TNBC ranges from 1.4–17% [28–30]. Although MedBC shares common genomic alterations with nonMedBC basal-like carcinoma, it is a distinct genomic entity within the basal-like spectrum harboring a higher rate of TP53

mutations [31, 32]. MedBC and IDC with medullary features are associated with germline mutations in the BRCA1 gene. Among BRCA1-associated breast cancers, 7.8% to 19% are medullary carcinomas, and 35% to 60% show the presence of medullary features [33]. This rate contrasts with the presence of only 2% medullary carcinomas among sporadic, non–BRCA-associated tumors [33].

Mean age at presentation is often younger than that for IDC, with a mean age ranging from 45 to 54 years [34]. Medullary carcinoma is unicentric in most of the patients [34] although bilateral tumors are common when family history is present [35]. Overall, the incidence of nodal involvement is lower than other carcinomas of the breast [36].

The treatment for MedBC is similar to IDC overall. The division into typical and and those with medullary features does not modify treatment options and has only prognostic significance [37]. Overall, the prognosis of MedBC appears to be slightly better than that of grade-matched invasive carcinoma of no special type, despite its aggressive cytologic features [28, 38, 39]. In a case series published in 2005 including 46 cases from 1971 to 2001, the 10-year-distant relapse-free survival was 95% [29]. More recently, evidence suggests prognosis in these tumors is more consistently related to immune response which may have its own genetic signature, rather than the histologic subtype, characterized by a high level of expression of immune-related and inflammation genes [4, 32, 39–43].

Apocrine Carcinoma—Apocrine carcinoma is seen in 0.3–1% of all breast cancers [44, 45]. Histologically, these tumors have abundant eosinophilic granular cytoplasm, enlarged nuclei with prominent nucleoli (apocrine morphology) in >90% of tumor cells, usually high-grade cytologic features, and commonly co-exists with *in situ* disease of same differentiation [46]. These tumors are typically negative for ER, PR and HER amplification (*i.e.*, TNBC) and stain positive for GCDFP15 and androgen receptor [45]. These are more common in patients with a germline PTEN mutations (i.e. Cowden's syndrome) [47]. Recent genomic analyses of 18 patients with apocrine carcinoma of the breast found mutations in PIK3CA (72%), PTEN (33%) and p53 (28%). In addition, a novel FGFR2-TACC2 translocation was identified that is potentially actionable [48]. Other analyses have found losses at 1p, 16q, and 17q and gains at 2q and 13q [49].

Clinically, patients with apocrine carcinomas of the breast are more likely to be older age at diagnosis, and are less likely to be African American [50]. Like other TNBC patients, those with apocrine carcinomas are treated with chemotherapy, although they have a better overall survival compared to other patients with TNBC with a hazard ratio of ~0.7 [50, 51]. Recently, responses to anti-androgen therapy has been reported in patients with metastatic apocrine carcinomas [52, 53].

Low Grade Adenosquamous Carcinoma—Metaplastic breast cancer is typically an aggressive breast cancer with poor prognosis (see below). Low grade adenosquamous carcinoma (LGASC) of the breast is a very rare tumor (< 150 cases reported in the literature) that was originally described by Rosen and Ernsberer as a low grade variant of adenosquamous metaplastic breast cancer [54]. Histologically, these tumors have small tubular glands or solid nests of cells with squamous differentiation in a background of

sclerosing stroma, often arising in association with benign complex sclerosing lesions/radial scars, making their diagnosis challenging to distinguish from their benign mimic – squamous metaplasia in radial scars [54–57]. Immunohistochemistry shows LGASC to most commonly be ER negative [57]. A genomic analysis of LGASC cases using targeted sequencing of 50 genes found frequent activating mutations in the PIK3CA gene (11 of 21 cases) [58]. Mutations in GNAS, KIT, CDKN2A and PTEN were seen in one tumor each. Unlike the more aggressive forms of metaplastic breast cancer described below, no mutations in p53 or EGFR amplification were seen [58].

Clinically, LGASCs have been reported in patients from 19 to 88 and are generally treated with excisional biopsy or mastectomy [59, 60]. While axillary evaluation has not been routinely performed, the frequency of axillary metastases is low and distant metastases is also rare [59, 60]. Local recurrence is seen after excisional biopsies but most of these patients can be successfully treated with re-excision with long disease-free survivals reported. In the largest series reported by Van Hoeven, only two of thirty two patients died of cancer, one from a local recurrence that directly invaded the hemithorax (VH) [60]. The role of radiation or chemotherapy has not been demonstrated for these tumors and surgical management remains the treatment [59, 60].

Secretory Carcinoma—Secretory carcinoma of the breast is a rare cancer representing <1% of all breast cancer with a slightly younger median age of 53–56 compared to other types of breast cancer and has been reported in patients as young as 8 years old [61–63]. Histologically, secretory carcinoma has cells with low-grade nuclei and moderate amount of cytoplasm, intracellular and extracellular secretory material, arranged in glandular, cystic, and solid nests, separated by collagen bands creating a characteristic “honeycomb” pattern [61, 64]. While the initial publications described these as negative for ER, PR and HER2 amplification (*i.e.*, TNBC) [62], a more recent survey of 246 cases in the SEER database found that 64% were classified as ER+ [63]. However, in a recent publication from Hoda *et al.* evaluating 14 cases of secretory cancer, 6 (43%) were ER+, but in 5 of 6 of the ER+ tumors, <10% of the cells stained positive and the last one had <50% of the cells staining positive [61]. Similarly, PR expression was seen in 3 of the 14 cases but again the expression was seen in < 5% of the cells [61]. Thus, these cancers can weakly express ER and PR. Secretory cancers almost always lack HER2 amplification [61–63], although there are rare reported cases with HER2 amplification. The most striking molecular feature of secretory cancer is that they almost universally contain a chromosomal translocation t(12;15)(p13;q25) which results in expression of a fusion protein ETV6-NTRK3 between the E26 transformation-specific translocation variant 6 (ETV6) transcription factor and the neurotrophin-3 receptor tyrosine kinase (NTRK3) [65]. Small molecular kinase inhibitors have been approved by the U.S. FDA for treatment of patients with metastatic NTRK fusion cancers, agnostic of the tissue of origin [66]

Secretory carcinomas most commonly present with a palpable breast mass and are treated either with breast conserving therapy or mastectomy [61–63]. Positive lymph nodes are found in 32–35% of patients but distant metastases are rare at presentation, found in ~2% [62, 63]. Despite the ER poor/TNBC phenotype of these cancers, patients with secretory breast cancer have an excellent overall prognosis with cancer specific survival of >90% at 10

years [62, 63]. Few patients develop metastatic recurrences [61–63]. Many patients who receive lumpectomy also are treated with radiation. In one retrospective analysis of 83 patients, the cancer specific survival was better in those that received radiation (97% at 5 and 10 years) compared to those who did not receive radiation (93% and 89% at 5 and 10 years, respectively). These differences were not statistically significant so that the role of radiation remains undetermined. Chemotherapy in the adjuvant setting has been used but it is unclear if there is any benefit [61–63]. Several reports treating patients in the metastatic setting describe the secretory cancers as chemotherapy resistant [67, 68]. Clinical benefit has been reported in patients with metastatic secretory breast cancer treated with kinase inhibitors targeting the ETV6-NTRK3 fusion protein [61].

Rare breast cancers with poor prognosis

Pleomorphic Lobular Carcinoma—Pleomorphic lobular carcinoma (PLC) is recognized as a variant of ILC. PLC is an uncommon diagnosis, accounting for 10–15% of ILCs and only 1% of all breast cancers diagnosed [69]. Pathologic findings are similar to classic ILC in the discohesive quality of the cell aggregates and cytologic features of intracytoplasmic mucin vacuoles and abundant cytoplasm. PLC differs in that high-grade cytologic features, such as mitotic activity, hyperchromasia, nuclear membrane irregularities, and prominent nucleoli are observed [70]. Unlike classical ILC, which tends to be uniformly HR+ and have a luminal A molecular subtype, PLC has much more variability. Most PLCs retain ER and PR expression and a luminal B molecular subtype, but unlike classical ILC a significant portion have HER-2 over-expression or are classified as TNBC [71, 72]. In addition to a lack of hormone responsiveness, PLCs tend to display a more aggressive growth pattern [73]. A large retrospective study of women with ILC found that women diagnosed with PLC had a greater incidence of poorly differentiated disease, larger primary tumors, and a higher incidence of node-positivity than classical ILC [74]. Though PLC retains the classical pattern of invasive lobular carcinoma metastatic spread, there is evidence that PLC is more prone to develop metastatic spread [75]. These findings are confirmed in multiple smaller studies, with several of these studies also showing worse overall survival [76, 77]. Due to its rarity, no specific management guidelines exist. PLC is treated in a similar manner to invasive ductal carcinoma. The approach to definitive management for localized disease often includes aggressive surgical resection, usually in the form of a mastectomy [75]. The roles of endocrine therapy with or without adjuvant chemotherapy are unclear for early stage ILC and PLC. In a single-institution retrospective study, use of Oncotype DX breast cancer assay produced a significantly different recurrence score (RS) distribution in ILC when compared to IDC, with only 2% of ILC having a high RS [78]. A significant difference in the distribution of recurrence scores were noted between ILC and PLC where approximately 42% of ILC had low RS while all PLC in this study had intermediate RS. Though sample size is lacking, Mahtani *et al.* describe a series of four patients with HER-2 positive PLC who experienced durable clinical responses to HER-2 targeted therapy that range from 4–9 years [79].

Inflammatory Breast Carcinoma—Inflammatory breast carcinoma (IBC) is a rare form of breast cancer with a particularly aggressive disease course. While it represents only 2–4% of invasive breast cancers, it accounts for 7–10% of breast cancer mortality [80]. It is a

clinical diagnosis rather than a histological subtype and is defined by meeting the following criteria: (1) rapid symptom onset of <6 months; (2) breast-associated skin changes of erythema, edema, warmth, and/or peau d'orange with or without an underlying mass; (3) skin changes encompassing at least one-third of the breast; (4) pathological tissue confirmation of an associated invasive breast cancer [81].

However, it does have a common—but not diagnostic—histologic correlate: dermal lymphatic congestion by tumor emboli. This variation of lymphovascular space invasion is the underlying etiology of the classical presentation of IBC with diffuse breast-associated skin changes. At the molecular level, IBCs are heterogenous and can present with any breast cancer subtype. In terms of distribution, nearly half of IBCs are ER and PR positive and HER-2- [82, 83]. Regardless of the receptor subtype, a diagnosis of IBC is associated with a poor prognosis. Patients with IBC have a higher risk of locoregional recurrence, a greater risk of distant metastases, and a shorter overall survival as compared to non-inflammatory breast cancer [84, 85].

Following complete systemic staging work-up, neoadjuvant anthracycline- and taxane-based chemotherapy with the addition of HER-2 directed therapy as clinically appropriate based on receptor status is recommended [81]. This is followed by definitive surgical treatment with a total mastectomy with level I and II axillary lymph node dissection and radiation therapy to the chest wall, infraclavicular region, supraclavicular areas, internal mammary nodes, and the axillary bed. Adjuvant HER-2 targeted or hormonal therapy follow as clinically appropriate by receptor status. Based on multidisciplinary expert panel opinion, breast conservation surgery is strongly not advised [81, 86]. If the cancer fails to respond to neoadjuvant therapy, these patients are then treated similarly to recurrent or metastatic disease with systemic chemotherapy and/or targeted therapy.

Metaplastic Carcinoma—Metaplastic breast cancer (MBC) is a rare and aggressive form of breast cancer, representing <1% of all breast cancer [87–90]. MBC is comprised of a heterogeneous group of tumors with epithelial differentiation not native to the breast such as squamous or choriocarcinomatous and low-grade adenosquamous (see above), as well as those that display mesenchymal-type cytologic features to include spindled cells, bone, cartilage, or a mixture of morphologies [87–90]. The recent WHO classification of breast tumors includes adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, and mixed metaplastic carcinoma under the category of MBC [87, 88].

The tumors can occur in patients with or without a prior history of breast cancer [91]. The majority (~90%) of MBC lack expression of ER and PR and are HER2- and thus are clinically classified as TNBC [90, 92–96] [97]. Clinically at diagnosis, MBC is characterized by large tumors (*e.g.*, 70.5% T2/T3 compared to 34.8% for IDC), high stage (*e.g.*, 65.5% Stage II/III compared to 45.7% for IDC), and high grade (*e.g.*, 67.8% grade 3 compared to 38.8% for IDC) [90, 98, 99]. Patients with MBC are on average older at diagnosis and more likely to be African American or Hispanic than those with IDC [90]. By gene expression classification, MBCs are basal-like tumors [95, 100].

Only limited molecular analyses of MBC have been performed to date. EGFR amplification has been described in ~25% MBC [94, 101]. Copy number variations (CNV) in MBC that are distinct from those of IDC have been reported, supporting the idea that MBC is a unique subtype of breast cancer [102]. Also, mutations in the catalytic domain of PIK3CA in 21% (4/19) of MBC (compared to 5% in other TNBC) have been reported [102]. Mutations of p53 in 28% (4/14) MBC have been reported in one study compared to 80% p53 mutations in basal like tumors described in the TCGA study [103, 104]. Additional genomic abnormalities observed include TERT promoter mutations and X-Chromosome inactivation [89, 105]. These data suggest that there are potential molecular targets (e.g. EGFR or PIK3CA) in MBC however a comprehensive survey of the molecular abnormalities in MBC has not been undertaken to date.

While there are isolated reports of good responses to chemo therapy in patients with MBC, the general experience has been that these tumors are resistant to the standard chemotherapeutic agents used in breast cancer patients [92, 93, 98, 106–108]. For example a retrospective analysis of response to neoadjuvant therapy in breast cancer patients found that there were no pathological complete responses (pCRs), 35.7% clinical responses (all partial responses), and 50% progressive disease (PD) in patients with MBC [93]. By contrast patients with IDC overall had a 22.6% pCR rate, 85% clinical response rate (33% complete and 52% partial responses), and only 2.5% with PD [93]. The poor rate of response to chemotherapy in MBC is in striking contrast to other types of TNBC where high rates of response including pCRs as high as 40–67% have been reported [109–111]. Also, low (~10–20%) response rates to chemotherapy are seen in metastatic MBC compared to IDC where response rates as high as 60–70% have been reported [98, 107, 112, 113]. In keeping with the aggressive features of the tumors and the poor response to standard chemotherapy, patients with MBC have a high rate of disease recurrence, disease progression, and a lower overall survival than patients with IDC [92, 96, 98, 108, 113, 114]. Most studies have consistently shown 5 year DFS for early stage MBC of <50% while IDC and TNBC typically have 5 year DFS of >70% [92, 98, 108, 113, 114].

In recent work, Basho *et al.* tested the combination of liposomal doxorubicin, bevacizumab, and an mTOR inhibitor (temsirolimus or everolimus) in a cohort of 52 patients with triple negative metaplastic breast cancers. They found the overall objective response rate (ORR) was 21% (4 CR and 7 PR) and a clinical benefit rate (ORR + SD for at least 6 months) of 40% [115]. Interestingly, in a subset of 43 patients with evaluable tissue, patients with a genetic aberration in the PI3K pathway had an ORR of 31% vs 0% in those who did not. However, the clinical benefit rate was the same in both those with or without PI3K pathway aberrations (44% vs 45%, respectively) [115].

Neuroendocrine Carcinomas—Primary neuroendocrine breast carcinomas (NEBC) have a low reported incidence, accounting for less than one percent of the total number of breast cancers diagnosed in the United States [116, 117]. This is due to the rarity of diagnosis as well as evolving diagnostic criteria. The WHO officially defined NEBCs as having neuroendocrine markers in at least 50% of tumor cells in 2003. This was further refined in 2019 with the subdivision of neuroendocrine tumors into two groups: (1)

neuroendocrine tumor, and (2) neuroendocrine carcinoma (NEBC) [4]. The latter is discussed below.

NEBCs are high-grade and most present with neuroendocrine morphology with hyperchromatic cells with high nuclear-to-cytoplasmic ratio, variably course chromatin, diffuse uniform reactivity for neuroendocrine markers, including synaptophysin, chromogranin, CD56, neuron specific enolase. They are nearly indistinguishable from their counterparts in the lung (small cell and large cell carcinomas) with an *in situ* component as the best evidence for a primary tumor. A significant proportion (30–50%) of NEBCs are HR + [4]. Studies of HER2 amplification are evolving but appears that only a minor fraction of NEBC are HER2+ [116, 117]. When classified according to molecular subtype, NEBCs were nearly even in distribution between the luminal subtypes A and B [118].

Most cases present as an asymptomatic, isolated breast mass. Unlike gastrointestinal neuroendocrine tumors, only a subset of NEBCs are functionally active and capable of causing carcinoid syndrome. One of the largest studies to date, based on the SEER database, compared NEBCs (n=142) with invasive breast carcinomas (n=381,644) [116]. This study showed strong evidence that NEBCs represent a more aggressive tumor phenotype, with significantly higher tumor grades, TNM stage, and incidence of positive regional lymph nodes at time of diagnosis. These findings translated into a shorter overall survival and disease-specific survival when compared to invasive breast carcinomas. This aggressive phenotype has been confirmed in smaller scale studies [118, 119]. Standardized treatment for NEBCs does not exist due to its rarity. Most case reports in the literature approach NEBCs similarly to IDC, with definitive surgical treatment, where applicable, systemic anthracycline- and taxane-based chemotherapy, and subsequent endocrine therapy. Others have approached NEBCs, particularly of the poorly differentiated/small cell carcinoma subtype, with platinum drugs and etoposide [120].

Micropapillary Carcinoma—Micropapillary carcinoma of the breast (MCB) is a rare and aggressive subtype IDC. It accounts for approximately 0.9–2.0% of all diagnosed invasive breast carcinomas [4]. Histologically, it presents as clusters of malignant cells that lack fibrovascular cores but maintain clear stromal spaces, creating the appearance of a papillary structure, often with reverse polarity. Apocrine features are common with high nuclear grade. The majority of MCBs are ER+, PR+, and HER2+ [121–123]. At the chromosomal level, MCBs are associated with recurrent gains of 8q, 17q, and 20q as well as deletions of 6q and 13q. As compared to ER-expressing IDCs, Marchio *et al.* found MCBs to have high expression of cyclin D1, *MYC* amplifications, and high proliferation indices [124]. Whole exome sequencing of a limited sample of MCBs showed the most common mutations to involve PIK3CA, TP53, and GATA3 [125].

Presentation of MCBs is similar to that of IDC. On mammography, it most often presents as a high-density mass with spiculated margins and associated microcalcifications [123]. These tumors are characterized by high incidence of lymphovascular invasion and axillary lymph node metastasis [122, 126]. Despite these aggressive clinical features, it is unclear whether the histological diagnosis of MCB translates to a decreased overall survival. In a retrospective study of matched patient pairs (n=308 pairs), MCB had worse recurrence-free

survival for both local and distant disease when compared to IDC [127]. However, this failed to translate to a significant difference in overall survival. Looking specifically at non-metastatic MCBs, Chen *et al.* found MCBs to have improved breast cancer-specific survival and overall survival as compared to IDCs despite confirming MCBs greater incidence of lymphovascular invasion and lymphatic progression [128]. Additional studies have noted a lack of significant difference in disease-specific survival and/or overall survival between MCBs and IDCs [128–131]. Histology-specific treatment guidelines do not exist and thus treatment is similar to IDC.

Rare breast cancers with unclear prognosis

Lipid Rich Carcinoma—Lipid rich carcinoma (LRC) is a rare subtype of breast cancer representing less than 1% of all breast cancers first described by Aboumrad, Horn and Fine in 1963 as “lipid secreting carcinoma” [132] and formally classified as unique sub-type in 2003 by the WHO [133] with only ~70 cases reported in the English literature to date [134, 135]. The WHO has since moved this under IDC as a distinct pattern [4].

Lipid rich pattern of IDC is similar to glycogen-rich in that it has clear cell histology with bubbly cytoplasm but differs in that the cytoplasmic composition is positive for Sudan black or oil red O rather than Periodic acid Schiff due to high lipid content. According to WHO classification 2012, the diagnosis of LRC of the breast requires no fewer than 90% of the cells contain abundant cytoplasmic neutral lipids [88].

In 2008 Shi *et al.* analyzed the clinicopathological data of 49 LRCs among 3,206 patients with breast cancer, none were ER+, five (10.2%) were PR+, and 35 (71.4%) were HER2+ [136]. Moreover, review of additional case reports showed 2 cases [137, 138] that were ER+ but that overall LRC tends to be ER/PR negative and HER2+.

The clinical characteristics of LRC are not well known and can be seen over a wide age in women ranging from 33 to 81 years with one report of a male patient [133, 134]. The presenting symptoms are usually a unilateral lump in the breast and rarely with nipple discharge [137]. The lump usually involves the upper outer quadrant of the breast with the equal incidence of occurrence in both breasts [138]. Treatment is typically performed on the basis of standard treatment protocols with chemotherapy, preferably taxane or platinum based [136], considered to be the most effective method given the propensity for these tumors to be ER/PR negative [135, 137]. Since HER2 overexpression is found in the majority of cases, these patients may also benefit from HER2 targeted treatment [137, 139].

In the above review of 49 cases by Shi *et al.*, lymph nodes metastases were reported in 38 patients (78%) [136]. Moreover, the 2- and 5-year survival rates were 64.6% and 33.2%, respectively [136]. Thus, lipid rich carcinoma of the breast is generally considered to be an aggressive phenotype of breast cancer with poor prognosis [135]. There remains no consensus on the prognostic factors with regard to lipid-rich breast carcinoma. The presence of positive axillary lymph nodes is a significant indicator for poor survival, while age, histological grade, tumor size, HER2 expression and Ki67 status remain controversial [136–138].

Oncocytic Carcinoma—Oncocytic carcinomas originate from varying anatomical sites but most commonly occur in endocrine and glandular epithelial cells, including the breast. The WHO classifies oncocytic carcinoma of breast as “uncommon” and another pattern of IDC [4]. The actual incidence is unknown due its exceedingly rare presence in the literature. There is some speculation that it is under reported due to an arbitrary separation between equivalent terminology of oncocytic and mitochondria-rich. It is characterized by an oncocytic pattern in which cells have abundant eosinophilic granular cytoplasm in more than 50% of cells [4]. It closely mimics apocrine differentiation but differs in several respects. First, oncocytic carcinoma is defined by a characteristic high density of mitochondria in the cytoplasm that can be quantified with immunohistochemical staining with anti-mitochondrion antibody. Apocrine differentiation also differs from oncotyic carcinoma in terms of HR staining. While oncocytic carcinoma appears to have variable HR expression, it is predominantly noted to have a luminal phenotype, expressing ER and PR and lacking androgen receptor (AR) [140–142]. Apocrine differentiation should be negative for ER and PR while positive for AR. Survival appears to be similar to that of IDC, though one case series reported a trend toward shorter survival [142]. No diagnosis-specific treatments exist at this time. Most case reports involve definitive surgical therapy only [143, 144]. Of note, oncocytic carcinomas of other anatomic variants have been reported to be resistant to radiation therapy; it is unclear whether this also applies to oncocytic carcinoma of breast

Sebaceous Carcinoma—Breast sebaceous adenocarcinoma is a rare and special type of invasive breast cancer, with as few as 20+ cases reported in the literature [145]. It was first described in 1977 as a morphological variant of the so-called lipid-secreting carcinoma [146]. The WHO defines primary sebaceous carcinoma of the breast based on sebaceous differentiation in at least 50% of cells in the absence of any evidence of originating in the cutaneous adnexa (2), however there can be a morphological spectrum ranging from “pure” forms to cases containing minor divergent differentiation(s): ductal and/or squamous [147]. It was also reclassified by the WHO as a distinct pattern of IDC [4].

Breast sebaceous adenocarcinoma has a wide phenotypic spectrum with cases that are HR+, HER2+, and triple-negative tumors [148]. Review of the literature lists the proportions of positivity for ER, PR, HER-2, p53, EMA, and GCDFP-15 at 64.71%, 58.82%, 13.33%, 66.67%, 88.89%, and 0.00%, respectively [145]. There is no association with microsatellite instability or Muir-Torre syndrome as there are with sebaceous neoplasms in other organs [147].

Breast sebaceous carcinoma typically occurs in middle-aged women, with a median age of 65 years and a range from 25–80 [145, 149]. The clinical features of some breast sebaceous carcinoma tumors are very similar to those of breast fibroadenoma, and thus are sometimes removed as benign lesions [145]. The incidence rate of lymph node metastasis in breast sebaceous carcinoma is 50%, often with 1–3 lymph node metastases [145]. It is an extremely rare tumor; hence, its true incidence, prognosis, and optimal treatment are yet to be determined however, most breast sebaceous carcinoma belong to the luminal subtype, which has a good prognosis but there have been cases of node-negative tumors that developed local recurrence and metastasis suggesting there may be aggressive forms that mandate close follow up [145, 149]. Furthermore, it is unknown if these cases behave

differently from those of lipid-rich carcinoma which bears morphologic resemblance to sebaceous adenocarcinoma [147].

Glycogen-rich Clear Cell Carcinoma—Glycogen-rich clear cell carcinoma (GRCCC) of breast is a rare patter of IDC [4]. Descriptions regarding the patient population, incidence, survival, and prognosis lack consistency due to the lack of large volume trials. Previously, GRCCC of breast was noted to account for between 0.9–3.0% of all diagnosed breast carcinomas based on a limited number of cases [150]. However, a more recent study involving the SEER database reported this subtype to be even more rare, with an incidence of 0.01% following review of over one million clinical cases of breast cancer [151]. Histologically, GRCCC of breast is characterized by cytoplasmic accumulation of glycogen in greater than 90% of tumor cells. The nomenclature refers to the resulting clear appearance of glycogenated cytoplasm on hematoxylin and eosin staining following formalin fixation, the presence of which can be confirmed by Periodic acid-Schiff positivity [150, 151]. Though variable expression patterns have been noted in case reports, GRCCC of the breast are more frequently ER, PR and HER2 negative with a significantly higher tumor grade than their non-GRCCC breast cancer counterparts [151]. Otherwise, patient presentation was similar.

The prognosis conferred by the GRCCC of breast diagnosis remains controversial, with several small studies showing inconsistent outcomes. Per the largest study to date through the SEER database, the GRCCC subtype conferred a significantly worse outcome. Median overall survival was significantly shorter in GRCCC of breast vs non-GRCCC breast carcinomas (158 m vs. 176 m) despite adjusting for age, disease stage, tumor grade, receptor status, or treatment [151]. Despite worse overall survival, there are no pathology-specific guidelines for treatment. In the SEER database, most patients were treated with surgery and almost half received radiation therapy. Subgroup analysis suggested that more conservative surgical treatment followed by radiation therapy improved outcomes in GRCCC breast patients when compared to surgical intervention alone [151].

Mucinous Cystadenocarcinoma—Mucinous cystadenocarcinoma (MCA) of breast is a histologically distinct form of mucinous carcinoma that was first described in 1998 and just added to the WHO classification [4, 152]. It is exceedingly rare, being described in less than 30 case studies thus far. No large-scale studies exist. Morphologically, MCA of the breast is similar to the pancreatic and/or ovarian counterpart [4]. It contains abundant cysts that are lined by tall columnar cells of a mucinous differentiation with mild atypia in a single or pseudostratified arrangement without myoepithelial cells, and extracellular mucin is present. It has a characteristic immunophenotype of CK7+/CK20-/CDX2-, contrary to tumor of the same histology from other organs, and generally lacks expression of ER and PR [152, 153]. Only a few case studies have investigated HER2 amplification and rarely show positivity [154, 155]. Genomic information is limited due to the rarity of this pathology, but most cases show TP53 over-expression and high proliferation index [155].

Presentation occurs most often in the post-menopausal setting, and the diagnostic work-up is similar to that of invasive ductal carcinoma. However, one caveat exists. Due to the rarity of MCA of the breast, the diagnostic work-up must also include ruling out the more common

possibility that the breast lesion represents a metastatic mucinous carcinoma originating from the ovary or the pancreas. While typically TNBC, MCA of breast is associated with an indolent growth pattern and an overall favorable prognosis [153]. However, this must be interpreted with caution due to the paucity of available reported cases in the literature.

Conclusions

Breast cancer is a collection of diseases, including many rare subtypes with distinct histology and clinical features. The approach to some of these has been established (*e.g.*, the good prognosis ER+ tubular and mucinous tumors or inflammatory cancers). In others, the treatment mirrors the approach to the more common types (*e.g.*, apocrine carcinomas are treated like other TNBC). However, many do not have well defined clinical guidelines and are treated by extrapolation from the more common cancer types.

Acknowledgements

This work was supported in part by the Intramural Research Program of the Center for Cancer Research, NCI, NIH.

References

1. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol 2005;23(29):7350–60. [PubMed: 16145060]
2. Sharpiro C, Barsky SH. Infiltrating carcinomas of the breast: Not one disease. In: Bland KI, Copeland, editors. The Breast: Comprehensive management of benign and malignant disease. 1. Philadelphia, PA: Saunders Elsevier; 2009. p. 231–47.
3 ●●. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869–74. [PubMed: 11553815] This landmark paper identified molecular subtypes of breast cancer including luminal A, luminal B, basal and HER2 enriched based on the gene expression patterns, and is the basis for preclinical and clinical trial approaches to breast cancer.
4 ●●. WHO Classification of Tumours Editorial Board. Breast Tumours: World Health Organization classification of tumours. 5th ed. Lyon, France: IARC Press; 2019.The WHO classification of breast cancer is the reference for all pathology analysis and classification.
5. Di Saverio S, Gutierrez J, Avisar E. A retrospective review with long term follow up of 11,400 cases of pure mucinous breast carcinoma. Breast Cancer Res Treat. 2008;111(3):541–7. [PubMed: 18026874]
6. Marrazzo E, Frusone F, Milana F, Sagona A, Gatzemeier W, Barbieri E, et al. Mucinous breast cancer: A narrative review of the literature and a retrospective tertiary single-centre analysis. Breast. 2020;49:87–92.
7. Nakata B, Kuroda K, Yoshida Y, Iimori N, Masuda G, Lee T, et al. Huge mucinous carcinoma of the breast in which doubling time was observed by computed tomography during 3 years without treatment. Breast Dis. 2018;37(4):215–8. [PubMed: 29562481]
8. Bae SY, Choi MY, Cho DH, Lee JE, Nam SJ, Yang JH. Mucinous carcinoma of the breast in comparison with invasive ductal carcinoma: clinicopathologic characteristics and prognosis. J Breast Cancer. 2011;14(4):308–13. [PubMed: 22323918]
9. Kim HS, Lee JU, Yoo TK, Chae BJ, Son D, Kim YJ, et al. Omission of Chemotherapy for the Treatment of Mucinous Breast Cancer: A Nationwide Study from the Korean Breast Cancer Society. J Breast Cancer. 2019;22(4):599–612. [PubMed: 31897333]
10. Limaiem F, Mlika M. Tubular Breast Carcinoma. StatPearls. Treasure Island (FL)2020.

11. Rakha EA, Lee AH, Evans AJ, Menon S, Assad NY, Hodi Z, et al. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. J Clin Oncol. 2010;28(1):99–104. [PubMed: 19917872]
12. McDivitt RW, Boyce W, Gersell D. Tubular carcinoma of the breast. Clinical and pathological observations concerning 135 cases. Am J Surg Pathol. 1982;6(5):401–11. [PubMed: 6289683]
13. Javid SH, Smith BL, Mayer E, Bellon J, Murphy CD, Lipsitz S, et al. Tubular carcinoma of the breast: results of a large contemporary series. Am J Surg. 2009;197(5):674–7. [PubMed: 18789411]
14. Sun JY, Zhou J, Zhang WW, Li FY, He ZY, Wu SG. Tubular carcinomas of the breast: an epidemiologic study. Future Oncol. 2018;14(29):3037–47. [PubMed: 29989443]
15. Romano AM, Wages NA, Smolkin M, Fortune KL, Atkins K, Dillon PM. Tubular carcinoma of the breast: institutional and SEER database analysis supporting a unique classification. Breast Dis. 2015;35(2):103–11. [PubMed: 25567000]
16. Page DL, Dixon JM, Anderson TJ, Lee D, Stewart HJ. Invasive cribriform carcinoma of the breast. Histopathology. 1983;7(4):525–36.
17. Liu XY, Jiang YZ, Liu YR, Zuo WJ, Shao ZM. Clinicopathological Characteristics and Survival Outcomes of Invasive Cribriform Carcinoma of Breast: A SEER Population-Based Study. Medicine (Baltimore). 2015;94(31):e1309.
18. Venable JG, Schwartz AM, Silverberg SG. Infiltrating cribriform carcinoma of the breast: a distinctive clinicopathologic entity. Hum Pathol. 1990;21(3):333–8. [PubMed: 2312110]
19. Zhang W, Zhang T, Lin Z, Zhang X, Liu F, Wang Y, et al. Invasive cribriform carcinoma in a Chinese population: comparison with low-grade invasive ductal carcinoma-not otherwise specified. Int J Clin Exp Pathol. 2013;6(3):445–57. [PubMed: 23412348]
20. Munzone E, Giobbie-Hurder A, Gusterson BA, Mallon E, Viale G, Thurlimann B, et al. Outcomes of special histotypes of breast cancer after adjuvant endocrine therapy with letrozole or tamoxifen in the monotherapy cohort of the BIG 1–98 trial. Ann Oncol. 2015;26(12):2442–9. [PubMed: 26387144]
21. Colleoni M, Rotmensz N, Maisonneuve P, Mastropasqua MG, Luini A, Veronesi P, et al. Outcome of special types of luminal breast cancer. Ann Oncol. 2012;23(6):1428–36. [PubMed: 22039080]
22. Colleoni M, Russo L, Dellapasqua S. Adjuvant therapies for special types of breast cancer. Breast. 2011;20 Suppl 3:S153–7. [PubMed: 22015285]
23. Suh YJ, Shin H, Kwon TJ. Natural History of Invasive Papillary Breast Carcinoma Followed for 10 Years: A Case Report and Literature Review. Case Rep Med. 2017;2017:3725391.
24. Zheng YZ, Hu X, Shao ZM. Clinicopathological Characteristics and Survival Outcomes in Invasive Papillary Carcinoma of the Breast: A SEER Population-Based Study. Sci Rep. 2016;6:24037.
25. Liu ZY, Liu N, Wang YH, Yang CC, Zhang J, Lv SH, et al. Clinicopathologic characteristics and molecular subtypes of invasive papillary carcinoma of the breast: a large case study. J Cancer Res Clin Oncol. 2013;139(1):77–84. [PubMed: 22932921]
26. Fakhreddine MH, Haque W, Ahmed A, Schwartz MR, Farach AM, Paulino AC, et al. Prognostic Factors, Treatment, and Outcomes in Early Stage, Invasive Papillary Breast Cancer: A SEER Investigation of Less Aggressive Treatment in a Favorable Histology. Am J Clin Oncol. 2018;41(6):532–7. [PubMed: 27819878]
27. Saita C, Goto R, Aruga T, Idera N, Honda Y, Horiguchi K, et al. Invasive papillary carcinoma treated with neoadjuvant endocrine therapy in which pathological complete response was achieved. BMC Res Notes. 2016;9:46. [PubMed: 26813772]
28. Mills MN, Yang GQ, Oliver DE, Liveringhouse CL, Ahmed KA, Orman AG, et al. Histologic heterogeneity of triple negative breast cancer: A National Cancer Centre Database analysis. Eur J Cancer. 2018;98:48–58. [PubMed: 29870876]
29. Vu-Nishino H, Tavassoli FA, Ahrens WA, Haffty BG. Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (BCT). Int J Radiat Oncol Biol Phys. 2005;62(4):1040–7. [PubMed: 15990007]
30. Marginean F, Rakha EA, Ho BC, Ellis IO, Lee AH. Histological features of medullary carcinoma and prognosis in triple-negative basal-like carcinomas of the breast. Mod Pathol. 2010;23(10):1357–63. [PubMed: 20581807]

31. de Cremoux P, Salomon AV, Liva S, Dendale R, Bouchind'homme B, Martin E, et al. p53 mutation as a genetic trait of typical medullary breast carcinoma. J Natl Cancer Inst. 1999;91(7):641–3. [PubMed: 10203285]
32. Vincent-Salomon A, Gruel N, Lucchesi C, MacGrogan G, Dendale R, Sigal-Zafrani B, et al. 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. [PubMed: 17417968]
33. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium. Lancet. 1997;349(9064):1505–10. [PubMed: 9167459]
34. Foschini MP, Eusebi V. Rare (new) entities of the breast and medullary carcinoma. Pathology. 2009;41(1):48–56.
35. 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):1365–85. [PubMed: 907958]
36. Dieci MV, Orvieto E, Dominici M, Conte P, Guarneri V. Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. Oncologist. 2014;19(8):805–13.
37. Eichhorn JH. Medullary carcinoma, provocative now as then. Semin Diagn Pathol. 2004;21(1):65–73. [PubMed: 15074561]
38. Graves L, 3rd, Stechschulte DJ, Morris DC, Lukert BP. Inhibition of mediator release in systemic mastocytosis is associated with reversal of bone changes. J Bone Miner Res. 1990;5(11):1113–9. [PubMed: 2270775]
39. Romero P, Benhamo V, Deniziaut G, Fuhrmann L, Berger F, Manie E, et al. Medullary Breast Carcinoma, a Triple-Negative Breast Cancer Associated with BCLG Overexpression. Am J Pathol. 2018;188(10):2378–91. [PubMed: 30075151]
40. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res. 2015;21(7):1688–98. [PubMed: 25208879]
41. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67. [PubMed: 21633166]
42. Purrington KS, Visscher DW, Wang C, Yannoukakos D, Hamann U, Nevanlinna H, et al. Genes associated with histopathologic features of triple negative breast tumors predict molecular subtypes. Breast Cancer Res Treat. 2016;157(1):117–31. [PubMed: 27083182]
43. Rakha EA, Aleskandarany M, El-Sayed ME, Blamey RW, Elston CW, Ellis IO, et al. The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast. Eur J Cancer. 2009;45(10):1780–7. [PubMed: 19286369]
44. Mills AM C EG, S MW, C MB, Atkins KA. Pure Apocrine Carcinomas Represent a Clinicopathologically Distinct Androgen Receptor-Positive Subset of Triple-Negative Breast Cancers. Am J Surg Pathol. 2016;40(8):1109–16. [PubMed: 27259012]
45. Yamazaki M, Nagata Y, Monji S, Shigematsu Y, Baba T, Shimokawa H, et al. Apocrine carcinoma of the breast. J UOEH. 2011;33(4):293–301. [PubMed: 22259834]
46. Vranic S, Schmitt F, Sapino A, Costa JL, Reddy S, Castro M, et al. Apocrine carcinoma of the breast: a comprehensive review. Histol Histopathol. 2013;28(11):1393–409. [PubMed: 23771415]
47. Banneau G, Guedj M, MacGrogan G, de Mascarel I, Velasco V, Schiappa R, et al. Molecular apocrine differentiation is a common feature of breast cancer in patients with germline PTEN mutations. Breast Cancer Res. 2010;12(4):R63. [PubMed: 20712882]
48. Sun X, Zuo K, Yao Q, Zhou S, Shui R, Xu X, et al. Invasive apocrine carcinoma of the breast: clinicopathologic features and comprehensive genomic profiling of 18 pure triple-negative apocrine carcinomas. Mod Pathol. 2020.
49. Jones C, Damiani S, Wells D, Chaggar R, Lakhani SR, Eusebi V. Molecular cytogenetic comparison of apocrine hyperplasia and apocrine carcinoma of the breast. Am J Pathol. 2001;158(1):207–14. [PubMed: 11141494]
50. Wu W, Wu M, Peng G, Shi D, Zhang J. Prognosis in triple-negative apocrine carcinomas of the breast: A population-based study. Cancer Med. 2019;8(18):7523–31. [PubMed: 31642210]

51. Arciero CA, Diehl AH, 3rd, Liu Y, Sun Q, Gillespie T, Li X, et al. Triple-negative apocrine carcinoma: A rare pathologic subtype with a better prognosis than other triple-negative breast cancers. J Surg Oncol. 2020.

52 ●. Bonnefoi H, Grellety T, Tredan O, Saghatchian M, Dalenc F, Mailliez A, et al. A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12–1). Ann Oncol. 2016;27(5):812–8. [PubMed: 27052658]

53 ●. Jongen L, Paridaens R, Floris G, Wildiers H, Neven P. Androgen deprivation by adrenal suppression using low-dose hydrocortisone for the treatment of breast carcinoma with apocrine features: a case report illustrating this new paradigm. Breast Cancer Res Treat. 2016;155(3):603–7. [PubMed: 26868122] These two papers demonstrate activity for anti-androgen therapy in apocrine TNBC.

54 ●. Rosen PP, Ernsberger D. Low-grade adenosquamous carcinoma. A variant of metaplastic mammary carcinoma. Am J Surg Pathol. 1987;11(5):351–8. [PubMed: 3578645] This paper defines this rare cancer subtype.

55. Denley H, Pinder SE, Tan PH, Sim CS, Brown R, Barker T, et al. Metaplastic carcinoma of the breast arising within complex sclerosing lesion: a report of five cases. Histopathology. 2000;36(3):203–9.

56. Gobbi H, Simpson JF, Jensen RA, Olson SJ, Page DL. Metaplastic spindle cell breast tumors arising within papillomas, complex sclerosing lesions, and nipple adenomas. Mod Pathol. 2003;16(9):893–901.

57. Rakha EA, Badve S, Eusebi V, Reis-Filho JS, Fox SB, Dabbs DJ, et al. Breast lesions of uncertain malignant nature and limited metastatic potential: proposals to improve their recognition and clinical management. Histopathology. 2016;68(1):45–56. [PubMed: 26348644]

58. Bataillon G, Fuhrmann L, Girard E, Menet E, Lae M, Capovilla M, et al. High rate of PIK3CA mutations but no TP53 mutations in low-grade adenosquamous carcinoma of the breast. Histopathology. 2018;73(2):273–83.

59. Soo K, Tan PH. Low-grade adenosquamous carcinoma of the breast. J Clin Pathol. 2013;66(6):506–11. [PubMed: 23268316]

60 ●. Van Hoeven KH, Drudis T, Cranor ML, Erlandson RA, Rosen PP. Low-grade adenosquamous carcinoma of the breast. A clinocopathologic study of 32 cases with ultrastructural analysis. Am J Surg Pathol. 1993;17(3):248–58. [PubMed: 8434705] This paper is the largest clinicopathologic study of this rare tumor subtype

61. Hoda RS, Brogi E, Pareja F, Nanjangud G, Murray MP, Weigelt B, et al. Secretory carcinoma of the breast: clinicopathologic profile of 14 cases emphasising distant metastatic potential. Histopathology. 2019;75(2):213–24.

62. Horowitz DP, Sharma CS, Connolly E, Gidea-Addeo D, Deutsch I. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. Breast. 2012;21(3):350–3.

63. Jacob JD, Hodge C, Franko J, Pezzi CM, Goldman CD, Klimberg VS. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base. J Surg Oncol. 2016;113(7):721–5.

64. Li D, Xiao X, Yang W, Shui R, Tu X, Lu H, et al. Secretory breast carcinoma: a clinicopathological and immunophenotypic study of 15 cases with a review of the literature. Mod Pathol. 2012;25(4):567–75. [PubMed: 22157932]

65 ●. Tognon C, Knezevich SR, Huntsman D, Roskelley CD, Melnyk N, Mathers JA, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell. 2002;2(5):367–76. [PubMed: 12450792] This work identifies the ETV6-NTRK3 fusion gene and protein as a nearly universal driver mutation in secretory breast carcinoma.

66. Roviello G, D'Angelo A, Sciortino M, Mini E, Nobili S, De Logu F, et al. TRK fusion positive cancers: From first clinical data of a TRK inhibitor to future directions. Crit Rev Oncol Hematol. 2020;152:103011. [PubMed: 32521311]

67. Herz H, Cooke B, Goldstein D. Metastatic secretory breast cancer. Non-responsiveness to chemotherapy: case report and review of the literature. Ann Oncol. 2000;11(10):1343–7. [PubMed: 11106125]

68. Krausz T, Jenkins D, Grontoft O, Pollock DJ, Azzopardi JG. Secretory carcinoma of the breast in adults: emphasis on late recurrence and metastasis. Histopathology. 1989;14(1):25–36.
69. Al-Baimani K, Bazzarelli A, Clemons M, Robertson SJ, Addison C, Arnaout A. Invasive Pleomorphic Lobular Carcinoma of the Breast: Pathologic, Clinical, and Therapeutic Considerations. Clin Breast Cancer. 2015;15(6):421–5. [PubMed: 26209026]
70. Butler D, Rosa M. Pleomorphic lobular carcinoma of the breast: a morphologically and clinically distinct variant of lobular carcinoma. Arch Pathol Lab Med. 2013;137(11):1688–92. [PubMed: 24168512]
71. Cha YJ, Kim YH, Cho NH, Koo JS. Expression of autophagy related proteins in invasive lobular carcinoma: comparison to invasive ductal carcinoma. Int J Clin Exp Pathol. 2014;7(6):3389–98. [PubMed: 25031766]
72. Varga Z, Zhao J, Ohlschlegel C, Odermatt B, Heitz PU. Preferential HER-2/neu overexpression and/or amplification in aggressive histological subtypes of invasive breast cancer. Histopathology. 2004;44(4):332–8. [PubMed: 15049898]
73. Jacobs M, Fan F, Tawfik O. Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature. Ann Diagn Pathol. 2012;16(3):185–9. [PubMed: 22197540]
74. Haque W, Arms A, Verma V, Hatch S, Brian Butler E, Teh BS. Outcomes of pleomorphic lobular carcinoma versus invasive lobular carcinoma. Breast. 2019;43:67–73.
75. Buchanan CL, Flynn LW, Murray MP, Darvishian F, Cranor ML, Fey JV, et al. Is pleomorphic lobular carcinoma really a distinct clinical entity? J Surg Oncol. 2008;98(5):314–7. [PubMed: 18668643]
76. Jung SP, Lee SK, Kim S, Choi MY, Bae SY, Kim J, et al. Invasive pleomorphic lobular carcinoma of the breast: clinicopathologic characteristics and prognosis compared with invasive ductal carcinoma. J Breast Cancer. 2012;15(3):313–9. [PubMed: 23091544]
77. Liu YL, Choi C, Lee SM, Zhong X, Hibshoosh H, Kalinsky K, et al. Invasive Lobular Breast Carcinoma: Pleomorphic Versus Classical Subtype, Associations and Prognosis. Clin Breast Cancer. 2018;18(2):114–20. [PubMed: 28720418]
78. Felts JL, Zhu J, Han B, Smith SJ, Truica CI. An Analysis of Oncotype DX Recurrence Scores and Clinicopathologic Characteristics in Invasive Lobular Breast Cancer. Breast J. 2017;23(6):677–86. [PubMed: 28097781]
79. Mahtani RL, Vogel CL. Pleomorphic lobular carcinoma of the breast: four long-term responders to trastuzumab--coincidence or hint? J Clin Oncol. 2008;26(35):5823–4. [PubMed: 19001341]
80. Lim B, Woodward WA, Wang X, Reuben JM, Ueno NT. Inflammatory breast cancer biology: the tumour microenvironment is key. Nat Rev Cancer. 2018;18(8):485–99. [PubMed: 29703913]
81 ●. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011;22(3):515–23. [PubMed: 20603440] This paper presents an international consensus for the diagnosis and treatment of inflammatory breast cancer
82. van Uden DJP, van Maaren MC, Strobbe LJA, Bult P, van der Hoeven JJ, Siesling S, et al. Metastatic behavior and overall survival according to breast cancer subtypes in stage IV inflammatory breast cancer. Breast Cancer Res. 2019;21(1):113. [PubMed: 31623649]
83. Wu SG, Zhang WW, Wang J, Dong Y, Sun JY, Chen YX, et al. Inflammatory breast cancer outcomes by breast cancer subtype: a population-based study. Future Oncol. 2019;15(5):507–16. [PubMed: 30378451]
84. Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD. Inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program of the National Cancer Institute, 1975–1992. Cancer. 1998;82(12):2366–72. [PubMed: 9635529]
85. Cristofanilli M, Valero V, Buzdar AU, Kau SW, Broglio KR, Gonzalez-Angulo AM, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. Cancer. 2007;110(7):1436–44. [PubMed: 17694554]
86. Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017;31:244–59.

87. Cooper CL, Karim RZ, Selinger C, Carmalt H, Lee CS, O'Toole SA. Molecular alterations in metaplastic breast carcinoma. J Clin Pathol. 2013;66(6):522–8. [PubMed: 23372178]

88. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO Classification of Tumours of the Breast. Lyon, France: IARC Press; 2012.

89. Leddy R, Irshad A, Rumboldt T, Cluver A, Campbell A, Ackerman S. Review of metaplastic carcinoma of the breast: imaging findings and pathologic features. J Clin Imaging Sci. 2012;2:21. [PubMed: 22616038]

90. Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol. 2007;14(1):166–73. [PubMed: 17066230]

91. Verma S, Cimino-Mathews A, Figueroa Magalhaes MC, Zhang Z, Stearns V, Connolly RM. A clinicopathologica analysis of 45 patients with metaplastic breast cancer. Cancer Res. 2012;72(24 suppl):527s.

92. Hennessy BT, Giordano S, Broglio K, Duan Z, Trent J, Buchholz TA, et al. Biphasic metaplastic sarcomatoid carcinoma of the breast. Ann Oncol. 2006;17(4):605–13. [PubMed: 16469754]

93. Nagao T, Kinoshita T, Hojo T, Tsuda H, Tamura K, Fujiwara Y. The differences in the histological types of breast cancer and the response to neoadjuvant chemotherapy: the relationship between the outcome and the clinicopathological characteristics. Breast. 2012;21(3):289–95. [PubMed: 22277312]

94. Reis-Filho JS, Milanezi F, Carvalho S, Simpson PT, Steele D, Savage K, et al. Metaplastic breast carcinomas exhibit EGFR, but not HER2, gene amplification and overexpression: immunohistochemical and chromogenic in situ hybridization analysis. Breast Cancer Res. 2005;7(6):R1028–35. [PubMed: 16280056]

95. Reis-Filho JS, Milanezi F, Steele D, Savage K, Simpson PT, Nesland JM, et al. Metaplastic breast carcinomas are basal-like tumours. Histopathology. 2006;49(1):10–21.

96. Lai HW, Tseng LM, Chang TW, Kuo YL, Hsieh CM, Chen ST, et al. The prognostic significance of metaplastic carcinoma of the breast (MCB) - A case controlled comparison study with infiltrating ductal carcinoma. Breast. 2013.

97. Jia Y, He C, Liu L, Sun L, Chen Y, Luo Y, et al. A Retrospective Study of the Imaging and Pathological Features of Metaplastic Breast Carcinoma and Review of the Literature. Med Sci Monit. 2019;25:248–58. [PubMed: 30618455]

98. Bae SY, Lee SK, Koo MY, Hur SM, Choi MY, Cho DH, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Cancer Res Treat. 2011;126(2):471–8. [PubMed: 21287362]

99. Barnes PJ, Boutilier R, Chiasson D, Rayson D. Metaplastic breast carcinoma: clinicalpathologic characteristics and HER2/neu expression. Breast Cancer Res Treat. 2005;91(2):173–8. [PubMed: 15868445]

100. Weigelt B, Kreike B, Reis-Filho JS. Metaplastic breast carcinomas are basal-like breast cancers: a genomic profiling analysis. Breast Cancer Res Treat. 2009;117(2):273–80. [PubMed: 18815879]

101 ●. Reis-Filho JS, Pinheiro C, Lambros MB, Milanezi F, Carvalho S, Savage K, et al. EGFR amplification and lack of activating mutations in metaplastic breast carcinomas. J Pathol. 2006;209(4):445–53. [PubMed: 16739104] This work domonstrates EGFR amplification, a potentially targetable abnormality, in ~25% of metaplastic breast cancer.

102 ●. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Cancer Res. 2009;69(10):4116–24. [PubMed: 19435916] This work domonstrates PIK3CA activating mutations in a subset of metaplastic breast cancer.

103. Cancer Genome Atlas N Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70. [PubMed: 23000897]

104. Lien HC, Lin CW, Mao TL, Kuo SH, Hsiao CH, Huang CS. p53 overexpression and mutation in metaplastic carcinoma of the breast: genetic evidence for a monoclonal origin of both the carcinomatous and the heterogeneous sarcomatous components. J Pathol. 2004;204(2):131–9. [PubMed: 15376261]

105. Krings G, Chen YY. Genomic profiling of metaplastic breast carcinomas reveals genetic heterogeneity and relationship to ductal carcinoma. Mod Pathol. 2018;31(11):1661–74. [PubMed: 29946183]
106. Amini A, Kakkis J, Reitherman R, Ibarra J, Sanati H. Near-complete pathological response with preoperative chemotherapy in a patient with metaplastic breast carcinoma. Anticancer Drugs. 2013;24(7):765–8. [PubMed: 23719538]
107. Chen IC, Lin CH, Huang CS, Lien HC, Hsu C, Kuo WH, et al. Lack of efficacy to systemic chemotherapy for treatment of metaplastic carcinoma of the breast in the modern era. Breast Cancer Res Treat. 2011;130(1):345–51. [PubMed: 21792625]
108. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol. 1999;10(4):413–9. [PubMed: 10370783]
109. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008;26(8):1275–81. [PubMed: 18250347]
110. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res. 2005;11(16):5678–85. [PubMed: 16115903]
111. Sikov WM, Dizon DS, Strenger R, Legare RD, Theall KP, Graves TA, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. J Clin Oncol. 2009;27(28):4693–700. [PubMed: 19720916]
112. Cardoso F, Bedard PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst. 2009;101(17):1174–81. [PubMed: 19657108]
113. Luini A, Aguilar M, Gatti G, Fasani R, Botteri E, Brito JA, et al. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Res Treat. 2007;101(3):349–53. [PubMed: 17009109]
114. Lester TR, Hunt KK, Nayeemuddin KM, Bassett RL, Jr., Gonzalez-Angulo AM, Feig BW, et al. Metaplastic sarcomatoid carcinoma of the breast appears more aggressive than other triple receptor-negative breast cancers. Breast Cancer Res Treat. 2012;131(1):41–8. [PubMed: 21331622]
115. Basho RK, Gilcrease M, Murthy RK, Helgason T, Karp DD, Meric-Bernstam F, et al. Targeting the PI3K/AKT/mTOR Pathway for the Treatment of Mesenchymal Triple-Negative Breast Cancer: Evidence From a Phase 1 Trial of mTOR Inhibition in Combination With Liposomal Doxorubicin and Bevacizumab. JAMA Oncol. 2017;3(4):509–15.
116. Wang J, Wei B, Albarracin CT, Hu J, Abraham SC, Wu Y. Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer. 2014;14:147. [PubMed: 24589259]
117. Zhu Y, Li Q, Gao J, He Z, Sun R, Shen G, et al. Clinical features and treatment response of solid neuroendocrine breast carcinoma to adjuvant chemotherapy and endocrine therapy. Breast J. 2013;19(4):382–7. [PubMed: 23721399]
118. Lavigne M, Menet E, Tille JC, Lae M, Fuhrmann L, Bonneau C, et al. Comprehensive clinical and molecular analyses of neuroendocrine carcinomas of the breast. Mod Pathol. 2018;31(1):68–82. [PubMed: 28884749]
119. Roininen N, Takala S, Haapasaari KM, Jukkola-Vuorinen A, Mattson J, Heikkila P, et al. Primary neuroendocrine breast carcinomas are associated with poor local control despite favourable biological profile: a retrospective clinical study. BMC Cancer. 2017;17(1):72. [PubMed: 28118820]
120. Yildirim Y, Elagoz S, Koyuncu A, Aydin C, Karadayi K. Management of neuroendocrine carcinomas of the breast: A rare entity. Oncol Lett. 2011;2(5):887–90.
121. Cui ZQ, Feng JH, Zhao YJ. Clinicopathological features of invasive micropapillary carcinoma of the breast. Oncol Lett. 2015;9(3):1163–6. [PubMed: 25663874]

122. Pettinato G, Manivel CJ, Panico L, Sparano L, Petrella G. Invasive micropapillary carcinoma of the breast: clinicopathologic study of 62 cases of a poorly recognized variant with highly aggressive behavior. Am J Clin Pathol. 2004;121(6):857–66. [PubMed: 15198358]

123. Yun SU, Choi BB, Shu KS, Kim SM, Seo YD, Lee JS, et al. Imaging findings of invasive micropapillary carcinoma of the breast. J Breast Cancer. 2012;15(1):57–64. [PubMed: 22493629]

124. Marchio C, Iravani M, Natrajan R, Lambros MB, Savage K, Tamber N, et al. Genomic and immunophenotypical characterization of pure micropapillary carcinomas of the breast. J Pathol. 2008;215(4):398–410. [PubMed: 18484683]

125. Dieci MV, Smutna V, Scott V, Yin G, Xu R, Vielh P, et al. Whole exome sequencing of rare aggressive breast cancer histologies. Breast Cancer Res Treat. 2016;156(1):21–32. [PubMed: 26907767]

126. Guo X, Chen L, Lang R, Fan Y, Zhang X, Fu L. Invasive micropapillary carcinoma of the breast: association of pathologic features with lymph node metastasis. Am J Clin Pathol. 2006;126(5):740–6. [PubMed: 17050071]

127. Yoon GY, Cha JH, Kim HH, Shin HJ, Chae EY, Choi WJ. Comparison of invasive micropapillary and invasive ductal carcinoma of the breast: a matched cohort study. Acta Radiol. 2019;60(11):1405–13.

128. Chen AC, Paulino AC, Schwartz MR, Rodriguez AA, Bass BL, Chang JC, et al. Prognostic markers for invasive micropapillary carcinoma of the breast: a population-based analysis. Clin Breast Cancer. 2013;13(2):133–9. [PubMed: 23246269]

129. Liu Y, Huang X, Bi R, Yang W, Shao Z. Similar prognoses for invasive micropapillary breast carcinoma and pure invasive ductal carcinoma: a retrospectively matched cohort study in China. PLoS One. 2014;9(9):e106564. [PubMed: 25188383]

130. Yang YL, Liu BB, Zhang X, Fu L. Invasive Micropapillary Carcinoma of the Breast: An Update. Arch Pathol Lab Med. 2016;140(8):799–805. [PubMed: 27472238]

131. Ye F, Yu P, Li N, Yang A, Xie X, Tang H, et al. Prognosis of invasive micropapillary carcinoma compared with invasive ductal carcinoma in breast: A meta-analysis of PSM studies. Breast. 2020;51:11–20.

132 ●. Aboumrad MH, Horn RC, Jr., Fine G. Lipid-secreting mammary carcinoma. Report of a case associated with Paget's disease of the nipple. Cancer. 1963;16:521–5. [PubMed: 14010714] This work first defined lipid rich carcinoma of the breast.

133. F.A. T, PE D, editors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon, France: IARC Press; 2003.

134. Kini H, Bhat S, Suresh PK, Thomas M. Clear cell carcinoma of breast lipid-rich variant. J Cancer Res Ther. 2019;15(5):1167–9. [PubMed: 31603128]

135. Oba T, Ono M, Iesato A, Hanamura T, Watanabe T, Ito T, et al. Lipid-rich carcinoma of the breast that is strongly positive for estrogen receptor: a case report and literature review. Onco Targets Ther. 2016;9:1641–6. [PubMed: 27051299]

136. Shi P, Wang M, Zhang Q, Sun J. Lipid-rich carcinoma of the breast. A clinicopathological study of 49 cases. Tumori. 2008;94(3):342–6.

137. Cong Y, Lin J, Qiao G, Zou H, Wang X, Li X, et al. Lipid-rich carcinoma of the breast: A report of two cases and a literature review. Oncol Lett. 2015;9(4):1729–32. [PubMed: 25789031]

138. Guan B, Wang H, Cao S, Rao Q, Wang Y, Zhu Y, et al. Lipid-rich carcinoma of the breast clinicopathologic analysis of 17 cases. Ann Diagn Pathol. 2011;15(4):225–32. [PubMed: 21396871]

139. Umekita Y, Yoshida A, Sagara Y, Yoshida H. Lipid-Secreting Carcinoma of the Breast: A Case Report and Review of the Literature. Breast Cancer. 1998;5(2):171–3. [PubMed: 11091643]

140. Damiani S, Eusebi V, Losi L, D'Adda T, Rosai J. Oncocytic carcinoma (malignant oncocytoma) of the breast. Am J Surg Pathol. 1998;22(2):221–30. [PubMed: 9500224]

141. Itagaki H, Yamamoto T, Hiroi A, Kawanishi K, Noguchi E, Ohchi T, et al. Synchronous and bilateral oncocytic carcinoma of the breast: A case report and review of the literature. Oncol Lett. 2017;13(3):1714–8.

142. Ragazzi M, de Biase D, Betts CM, Farnedi A, Ramadan SS, Tallini G, et al. Oncocytic carcinoma of the breast: frequency, morphology and follow-up. Hum Pathol. 2011;42(2):166–75. [PubMed: 21111455]

143. Costa MJ, Silverberg SG. Oncocytic carcinoma of the male breast. Arch Pathol Lab Med. 1989;113(12):1396–9. [PubMed: 2556089]

144. Marla NJ, Pai MR, Swethadri GK, Fernandes H. Male breast cancer-review of literature on a rare microscopic variant (oncocytic carcinoma). Indian J Surg. 2013;75(Suppl 1):240–2. [PubMed: 24426578]

145. Heng C, Wei T, Yingbing T, Hanzhong L. Clinicopathological characteristics of breast sebaceous adenocarcinoma. Pol J Pathol. 2018;69(3):226–33. [PubMed: 30509049]

146. van Bogaert LJ, Maldague P. Histologic variants of lipid-secreting carcinoma of the breast. Virchows Arch A Pathol Anat Histol. 1977;375(4):345–53. [PubMed: 199989]

147. Maia T, Amendoeira I. Breast sebaceous carcinoma-a rare entity. Clinico-pathological description of two cases and brief review. Virchows Arch. 2018;472(5):877–80. [PubMed: 29556777]

148. Acosta AM, Al Rasheed MRH, Xu H, Salibay C, Pins MR. Sebaceous carcinoma of the breast in a patient with a pathogenic BRCA2 (886delGT) mutation - focus on histopathologic and immunohistochemical features. APMIS. 2018;126(4):353–6. [PubMed: 29575201]

149. Kyriakos Saad M, Ghandour F, El Hachem G, Ghandour-Hajj F, El Hajj I, Saikaly E. Special type breast carcinoma: Sebaceous carcinoma of the breast; A case report and review of literature. Breast J. 2020.

150. Eun NL, Cha YJ, Son EJ, Gweon HM, Kim JA, Youk JH. Clinical Imaging of Glycogenrich Clear Cell Carcinoma of the Breast: A Case Series with Literature Review. Magn Reson Med Sci. 2019;18(3):238–42. [PubMed: 30175804]

151. Zhou Z, Kinslow CJ, Hibshoosh H, Guo H, Cheng SK, He C, et al. Clinical Features, Survival and Prognostic Factors of Glycogen-Rich Clear Cell Carcinoma (GRCC) of the Breast in the U.S. Population. J Clin Med. 2019;8(2).

152. Koenig C, Tavassoli FA. Mucinous cystadenocarcinoma of the breast. Am J Surg Pathol. 1998;22(6):698–703. [PubMed: 9630176]

153. Koufopoulos N, Goudeli C, Syrios J, Filopoulos E, Khaldi L. Mucinous cystadenocarcinoma of the breast: the challenge of diagnosing a rare entity. Rare Tumors. 2017;9(3):7016. [PubMed: 29081926]

154. Kucukzeybek BB, Yigit S, Sari AA, Rezanko T, Durak E, Sadullahoglu C. Primary mucinous cystadenocarcinoma of the breast with amplification of the HER2 gene confirmed by FISH - case report and review of the literature. Pol J Pathol. 2014;65(1):70–3. [PubMed: 25119013]

155. Petersson F, Pang B, Thamboo TP, Putti TC. Mucinous cystadenocarcinoma of the breast with amplification of the HER2-gene confirmed by FISH: The first case reported. Hum Pathol. 2010;41(6):910–3. [PubMed: 20338619]

Table 1

Rare tumors of the breast

Tumor histology	Frequency of all breast cancers
Rare breast cancers with good prognosis (ER and PR positive)	
Mucinous adenocarcinoma	2–3%
Tubular carcinoma	1–2%
Cribriform	0.4%
Invasive papillary	0.5%
Rare breast cancers with good prognosis (ER and PR negative or low)	
Medullary carcinoma	3–5%
Apocrine Carcinoma	0.3–4%
Low Grade Adenosquamous	<0.1%
Secretory Carcinoma	<1%
Rare breast cancers with poor prognosis	
Pleomorphic Lobular	<1%
Inflammatory carcinoma	2–4%
Metaplastic carcinoma	<1%
Neuroendocrine carcinomas of the breast	<1%
Micropapillary carcinoma	0.9–2
Rare breast cancers with unclear prognosis	
Lipid rich carcinoma	<0.1%
Oncocytic carcinoma	<0.1%
Sebaceous carcinoma	<0.1%
Glycogen rich carcinoma	0.9–3%
Mucinous cystadenocarcinoma	<0.1%