Breast carcinoma—rare types: review of the literature

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Invasive breast cancer is a heterogeneous disease in its presentation, pathological classification and clinical course. However, there are more than a dozen variants which are less common but still very well defined by the World Health Organization (WHO) classification. The rarity of many of these neoplasms does not allow large or randomized studies to define the optimal treatment. Many of the descriptions of these cancers are from case reports and small series. Our review brings updated information on 16 epithelial subtypes as classified by the WHO system with a very concise histopathology description and parameters helpful in the clinic. The aim of our review is to provide a tool for breast cancer caregivers which will enable a better understanding of the disease and its optimal approach to therapy. This may also stand as a clinical framework for a future understanding of these rarer breast cancers when gene analysis work is reported.

Key words: breast carcinoma, epithelial breast cancer, prognosis, treatment, triple negative, World Health Organization classification

Introduction

Invasive breast cancer is a heterogeneous disease in its presentation, pathological classification and clinical course. Most tumors are derived from mammary ductal epithelium, principally the terminal duct-lobular unit, and up to 75% of the diagnosed infiltrating ductal carcinoma are defined as invasive ductal carcinoma, not otherwise specified (IDC-NOS). The second most common epithelial type is invasive lobular carcinoma which comprises of 5%–15% of the group. However, there are more than a dozen variants which are less common but still very well defined by the World Health Organization (WHO) classification.

Recently, there has been an increased emphasis on the immunohistochemical and genetic profile of tumors and these classifications are evolving as a standard part of the diagnostic process. This novel approach pushes aside traditional descriptive definitions. An estrogen receptor (ER)-negative ductal (NOS) as well as adenoid cystic, acinic and metaplastic carcinoma may all receive the title of triple-negative disease and this may affect decision making for those less familiar with the nuances of the rare tumor types. Furthermore, the classification using gene expression profile was established using a cohort of ductal carcinoma NOS, without including cancers of special types. We therefore indicate that it is extremely important to highlight what is known about the different behavior of each tumor and gather together the published data with the goal of marrying the rare tumor types with a current molecular definition of breast cancer. The rarity of many of these neoplasms does not allow large or randomized studies to define the optimal treatment. Many of the descriptions of these cancers are from case reports and small series.

Our review brings updated information on 16 epithelial subtypes as classified by the WHO system [1] with a very concise histopathology description and parameters helpful in the clinic. The aim of our review is to provide a tool for breast cancer caregivers which will enable a better understanding of the disease and its optimal approach to therapy. This may also stand as a clinical framework for a future understanding of these rarer breast cancers when gene analysis work is reported.

Our review is based on Pubmed research updated to December 2008.

good prognosis, ER positive

Findings are summarized in Table 1.

tubular carcinoma

definition and epidemiology. The definition of a tubular carcinoma (TC) requires tumor purity with 90% tubular architecture. The characteristic finding histologically is open tubules composed of single layer of epithelial cells and cellular desmoplastic stroma. Nuclear grade is low. TC comprises of 0.7%–10.3% of the invasive epithelial breast cancer (IEC) and is more likely to occur in postmenopausal women. A population-based study of nodal metastases with 171 TC patients has found the proportion of cases with axillary nodal involvement at presentation to be lower in TC than in the grade 1 IDC group (12.9% and 23.9%, respectively) [2]. A smaller study (n = 33)
Table 1. Good prognosis typically ER-positive tumors

<table>
<thead>
<tr>
<th>Dominant HER-2 profile</th>
<th>Axillary lymph node involvement %</th>
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<tbody>
<tr>
<td>Tubular</td>
<td>Negative 13–25 [2, 3]</td>
</tr>
<tr>
<td>Invasive cribriform</td>
<td>Negative 14.3 [4, 5]</td>
</tr>
<tr>
<td>Pure mucinous</td>
<td>Negative ≤5 [6, 7]</td>
</tr>
<tr>
<td>Invasive solid papillary</td>
<td>Negative 0 [8]</td>
</tr>
<tr>
<td>Apocrine</td>
<td>50%</td>
</tr>
<tr>
<td>Solid neuroendocrine*</td>
<td>Negative 540 (n = 8) [10]</td>
</tr>
</tbody>
</table>

*Does not differ from other carcinomas and depends very much on its histological grade (see text).

reported on 25% of the cases to involve axillary nodes, most often micrometastases [3].

diagnostic imaging. TC has a variety of presentations, but it is mostly seen on mammography as a small spiculated mass and on sonography as an irregular mass with posterior acoustic shadowing [11].

immunohistology. Most of the cases are ER (>90%) and progesterone receptor (PgR) positive with a low proliferation index. HER-2 status (as determined by immunohistochemical staining or fluorescence in situ hybridization) and epidermal growth factor receptor are negative [12].

prognosis. Survival is not significantly different from that of the general population [13], even with positive axillary lymph nodes [14]. Five-year disease-free survival (DFS) for node-positive patients was 94% (n = 64). Interestingly, in this series, the 5-year DFS of those who did not receive systemic treatment was 100%.

invasive cribriform carcinoma

definition and epidemiology. These grade 1 tumors are characterized by a cribriform pattern in the majority of the invasive component. Tumors are divided into pure, classical and mixed forms of invasive cribriform carcinoma (ICC). In the classical and the mixed forms, <50% of the tumor consists of other histological types [4]. This tumor accounts up to 3.5% of the IEC, hence the data are based on case reports and small series. The mean age is 53–58 years. Page et al. reported 14.3% of the cases to involve axillary lymph nodes [4, 5].

diagnostic imaging. Stutz et al. reported on eight radiological cases. Only four were seen on mammography and the ultrasound was not entirely typical of breast carcinoma [15].

immunohistology. ER is positive in 100% and PgR in 69% of the cases [5]; HER-2 is negative [16].

prognosis. In an older series, the 5-year survival was 100% for pure and ≥50% ICC, 88% for <50% ICC and 78.3% for the IDC controls [5]. Ten-year breast-specific survival for the pure cases was 100% [4].

pure mucinous carcinoma

definition and epidemiology. The mucinous neoplasms are characterized by the production of abundant extracellular and/or intracellular mucin. The definition requires a mucinous component >50% of the lesion. The pure type contains mucin in all of the IDC. The WHO classification divides this tumor into three different subtypes: (i) mucinous carcinoma (ii) cystadenocarcinoma and columnar cell mucinous carcinoma and (iii) signet ring cell carcinoma [1]. Pure mucinous carcinomas represent 1%–4% of all breast cancers, with a reputation of presenting at one of the oldest median ages (71 years). Despite often having a large tumor size, the axillary lymph nodes are rarely involved; in a recent large series, 111 patients with mucinous breast cancer were identified. Ninety-six (86%) patients underwent nodal evaluation either by sentinel lymph node biopsy or by axillary dissection. Fourteen patients (13%) were found to have lymph node metastasis. Node positivity was associated with larger tumor size (mean 2.7 cm). None of the 31 patients with tumor size ≤1 cm had known lymph node metastasis (24 were node negative, and seven were not evaluated with sentinel lymph node biopsy or axillary dissection) [17]. In contrast to this study, there are reports on small tumors ≤1 cm presenting with at least a 5% incidence of nodal involvement [6, 7].

imaging. Pure mucinous carcinomas present an imaging challenge due to their isoechogenic appearance on ultrasound [18]. Typical magnetic resonance imaging (MRI) demonstrates a gradually enhancing contrast pattern and a very high signal intensity on T2 images [19, 20].

immunohistology. These are mostly well-differentiated lesions frequently associated with positive ERs (>90%) and PgRs (81.5%) and HER-2-negative disease. However, rare cases with HER-2-positive staining have been reported but these may need review.

prognosis. Mucinous tumors have a favorable prognosis with 5-, 10-, 15- and 20-year survival rates of 94%, 89%, 85% and 81%, respectively [7]. Node involvement was associated with a significant worse 5-year DFS or overall survival (OS) [13]. Other traditional parameters such as age, T size, nuclear grade and PgR status also significantly influence outcome [7].

invasive solid papillary carcinoma

definition and epidemiology. The literature is unclear whether solid papillary carcinoma (SPC) is a form of in situ carcinoma or a true invasive malignancy and the WHO classification defines invasive SPC as a separate entity. SPC characteristically has papillae with focal solid areas. Ductal carcinoma in situ (DCIS) is present in >75% of cases and lymphatic vessel invasion in one-third of the cases. The tumor comprises <1% to 2% of IEC and typically presents in postmenopausal women with only 15% of reported cases occurring under the age of 50. Otsuki et al. reported on 20 patients with pure SPC and no axillary lymph node involvement [8].

immunohistology. In total, 100% of the tumors are ER positive and HER-2 negative and 80%–100% are PgR positive. Almost all cases show positive staining for chromogranin and ~40% are also positive for synaptophysin [8, 21].

imaging. The sonographic features are indistinguishable from papillomas. The only differential finding between noninvasive and invasive papillary cancers was circumscribed margins [22].
apocrine carcinoma
definition and epidemiology. Microscopically, apocrine carcinomas (ACs) demonstrate the same architectural growth pattern as invasive ductal carcinomas of no special type, differing only in their cytological appearance. The cells are characterized by typical apocrine features with abundant eosinophilic granular cytoplasm and prominent/multiple nucleoli. There is no agreed definition and some pathologists now confirm their diagnosis by staining for gross cystic disease fluid protein-15 [9, 25]. Axillary lymph node incidence varies from <1% to 4% but there is extremely sparse information in the literature.
immunohistology. These tumors are reported as ER positive in 3.8%–60% of cases, PgR positive in 4.8%–40%, HER-2 positive in 50%, with a proliferation index of 6.9%–23.7% and p53 alteration in 46%–50%. Androgen receptors are positive in 56%–100% of AC [9].
prognosis. AC has a similar prognosis to IDC-NOS when matched for stage and grade [26].

neuroendocrine tumors
definition and epidemiology. Neuroendocrine (NE) was not recognized as a single entity until the last WHO’s classification. This classification differentiates between four different subtypes: (i) small-cell carcinoma (SCC); (ii) large-cell carcinoma; (iii) solid NE carcinoma; and (iv) atypical carcinoid tumor. Our experience shows that the NE differentiation has no prognostic influence and on the whole they behave as per their Nottingham grade [27]. For simplification, this section describes the solid neuroendocrine subtype (SN) which represents a better prognosis group. (The SCC subtype is described in the ‘poor prognosis, ER positive’ section.) The tumors consist of densely cellular, solid nests and trabeculae of cells separated by delicate fibrovascular stroma [1]. Prevalence is up to 0.5% of breast cancers. In a small series of eight patients, three presented with involved axillary lymph nodes.
immunohistology. As per the definition, there is synaptophysin or chromogranin immunohistochemical expression in >50% of the cells. Typically, these tumors present with ER- and PgR-positive and HER-2-negative status [10].
gene expression. Profile of endocrine carcinoma overlaps with those of mucinous carcinomas [28].
imaging. There is no specific imaging presentation in the limited number of SN tumors reported.
prognosis. The outcome of these cancers does not differ from other carcinomas and depends very much on its histological grade [27, 29]. The immunoprofile is reminiscent of the luminal A subtypes, and hence a good prognosis is expected, although we are cautious of this claim with the small number of cases reported.

good prognosis, ER negative

Findings are summarized in Table 2.

medullary carcinoma
definition and epidemiology. This carcinoma is composed of poorly differentiated cells with no glandular structures, scant stroma, circumscribed margins and a prominent lymphoplasmacytic infiltrate. If most but not all the features are present, the tumor is identified as ‘atypical medullary carcinoma’ (AMC) [1]. Medullary carcinoma (MC) comprises 1%–7% of IEC. In a large series of almost 1500 patients with MC, only 27% had involved nodes. Although MC is not an indication for BRCA gene screening, there are growing data that indicate that MC may correlate with BRCA1 gene mutation [30].
diagnostic imaging. MC commonly manifests as well-circumscribed masses. Magnetic resonance mammography appearance is nonspecific and often indicative of a benign lesion [35, 36].
immunohistology. MC shares common characteristics with the basal type breast cancer. Most of the tumors are hormone receptor and HER-2 negative and CKT 5/6 positive (94%) [30, 37]. MC but not AMC lacks Bcl-2 and there are data that show they differ in expression of human leukocyte antigen-DR, β2-microglobulin, E cadherin and beta-catenin compared with other tumors [38].
prognosis. Paradoxical to its histology features, MC usually has a good prognosis. In one series, 10-year distant relapse-free survival reached 95% [30]. In another study, 10-year OS was 85% for MC as compared with 68% in the IDC-NOS patients [39]. Studies are hampered by lack of reproducibility of the pathological diagnosis, small numbers of patients and poor statistical power.

secretory breast carcinoma
definition and epidemiology. Secretary breast carcinoma (SBC) is also known as juvenile carcinoma. This is an extremely rare tumor with limited data available. Two distinctive pathological characteristics of SBC are intracellular/extracellular secretion and granular eosinophilic cytoplasm of the neoplastic cells. Although secretory carcinoma may occur in adults, the median and mean age are 33 and

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<tr>
<th>HER-2 profile</th>
<th>Axillary lymph node involvement %</th>
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<tr>
<td>Medullary</td>
<td>Negative</td>
</tr>
<tr>
<td>Secretary</td>
<td>Negative</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>Negative</td>
</tr>
<tr>
<td>Acinic cell</td>
<td>Negative</td>
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ER, estrogen receptor.
immunohistochemistry. This subtype has the triple-negative phenotype (ER, PgR, and HER-2 negative). It has been demonstrated that SCs of the breast consistently harbor the t(12;15)ETV6-NTRK3 translocation [41].

prognosis. SCC has a favorable prognosis in children and adolescents but seems slightly more aggressive in older patients. Metastatic cases have been reported [1].

Adenoid cystic carcinoma

definition and epidemiology. Adenoid cystic carcinomas (ACCs) are characterized by a mixture of proliferating glands, myoepithelial cells and stromal/basement elements. Data in the literature are based on ~200 cases. The tumor represents 0.1% of breast carcinoma and is diagnosed predominantly in postmenopausal women. Pain is a prominent symptom due to neural involvement [42]. Most of the reports document a low proliferative fraction [46]. In another study, all (n = 18) cases were c-kit (CD-117) positive. MIB-1 antibody (monoclonal antibody that is immunoreactive with Ki-67) stains demonstrate low proliferative fraction [46].

prognosis. The 5-, 10- and 15-year OS rates were 85%–88%, 75% and 60%, respectively, for ACC. Millar et al. reported an incidence of 26% (n = 5) for second malignancies at 15 years. The majority of the second cancers were not within the treated or contralateral breast [33]. Metastases are rare and have been reported to spread many years from diagnosis and without prior nodal disease [45, 47]. The most frequent site of metastases is lung. Patients may live many years with metastases.

Acinic cell carcinoma

definition and epidemiology. Acinic cell carcinoma is considered as one of the types of salivary gland-like tumors of the breast that show serous differentiation. Eighteen cases have been reported in the literature. Ages range from 35 to 80 years. Three cases with positive lymph nodes are recorded [34].

imaging. A well-defined mass creates a differential diagnosis with MC, intracytic carcinoma and metastatic carcinoma [48].

immunohistochemistry. This neoplasm is characterized by the lack of ER, PgR and HER-2. Expression of markers such as amylase, lysozyme and chymotrypsin is usually seen as in acinic cells of the salivary glands. Stains positive for epithelial membrane antigen and S100 protein are frequently found.

prognosis. The literature categorizes this tumor as a favorable one; however, even within a short follow-up period, systemic and local recurrences were recorded. Larger series are required for definite conclusions [49].

poor prognosis, ER positive

Findings are summarized in Table 3.

High-grade small-cell NE carcinoma

The literature describes <40 cases of breast small cell NE carcinoma (SCC) but this may be underreporting. This neoplasm is similar to NE tumors presenting in the lung or with extrapulmonary areas and share the same tumor markers.

Diagnosis requires ruling out a nonmammary origin [53]. The presence of in situ component may be helpful but is not essential [50, 54]. Most patients are in the sixth or seventh decades of life and ~59% present with involved lymph nodes.

immunohistochemistry. As per the definition, it expresses NE markers, neurone-specific enolase, protein gene product 9.5, chromogranin and synaptophysin, in >50% of the cell population [1]. Most of the cases are positive for cytokeratin CAM5.2, AE1/3 and cytokeratin 7 as well. Surprisingly, the tumor often expresses ERs and PgRs and this correlates with the degree of differentiation; well-differentiated tumors are the more likely to express hormone receptors with a varied frequency of 0%–50%. Her-2 status is typically negative [55, 56].

imaging. Radiological findings are not specific but meet the criteria for a suspicious mass [57].

prognosis. SCC tumor is considered an aggressive tumor with a poor prognosis. However, there are some reports about long-term survival when the diagnosis is made early [58]. NE differentiation using synaptophysin, chromogranin A, and neuron-specific enolase had no prognostic influence [27].

Invasive micropapillary carcinoma

definition and epidemiology. Hollow aggregates of malignant cells and lymphatic invasion is a common feature of this tumor, ranging from 72.3% to 91% of cases [51]. The pure variant is extremely rare. Mean age is 52.5 years (range 33–78). As opposed to the pure SPC, ~70% of the patients present with involved axillary lymph nodes [51, 52].

immunohistochemistry. About two-thirds of the cases are ER positive and up to 68% are PgR positive, one-third to one-half of the patients present with HER-2-positive status and 66% with Bcl-2 positive. p53 overexpression was identified in 48% of the cases [51, 59]. No basal-like immunostaining pattern was detected [60].

imaging. Mammography is able to diagnose >80% of the cases. Masses appear with high density. The margins are commonly

Table 3. Poor prognosis typically ER-positive tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dominant HER-2 profile</th>
<th>Axillary lymph node involvement %</th>
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<tbody>
<tr>
<td>Small cell</td>
<td>Negative</td>
<td>59 [50]</td>
</tr>
<tr>
<td>Invasive micropapillary</td>
<td>≤50%</td>
<td>70 [51, 52]</td>
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ER, estrogen receptor.
speculated; however, in approximately one-third of the patients, indistinct or microlobulated margins were seen. Microcalcifications were present in 43.8% of patients. On sonography, masses are typically hypoechoic, with only 60% of the masses showing posterior acoustic shadowing [61].

**prognosis.** Carcinoma with micropapillary features harbors a poor survival. The amount of IMC component correlates strongly with the number of involved axillary lymph nodes. In the 5-year follow-up (range 4–199 months) of 98 patients, 10-year OS was 48% and breast-specific survival was 63.3%. The outcome of the patients did not differ significantly from infiltrating ductal carcinomas of similar node status [62, 63].

**poor prognosis, ERs negative**

Findings are summarized in Table 4.

**metaplastic carcinoma**

**definition and epidemiology.** This term is used for describing an adenocarcinoma tumor with a dominant involvement of a metastatic component which may be of epithelial origin such as squamous or adenocarcinoma with spindle cell differentiation or mesenchymal origin. Most of them are high grade [1]. Metaplastic carcinoma is usually diagnosed with T2 disease, with a mean size 3.4–4.4 cm and is commonly diagnosed in women >50 years of age. The incidence is <1% of all invasive breast carcinoma with a relative high proportion of African American or Hispanic women (20%) [67, 68]. Most studies report a lower rate of axillary nodal involvement than that is seen with IDC [64, 65].

**imaging.** No unique imaging features are found. Mammographically, either a circumscribed or an indistinct lesion is typical. On ultrasound, metaplastic carcinoma reveals more benign features, characterized by oval, round or lobular solid hypoechoic mass with circumscribed margins. On MRI, almost all the cases show T2 hypersignal which is related to the necrotic component [69, 70].

**immunohistochemistry.** Most of these high grade neoplasms show a basal-like phenotype, few being positive for hormone receptors or HER-2 over-expression (0–8%) [69, 71].

**prognosis.** These tumors have a high metastatic potential. More than 50% of these tumors are associated with local or distal recurrence. The spread is hematogenous rather than lymphatic. Hennessy et al. found a median OS of 37 months [72]. The median survival from detection of metastatic disease was 8–12 months [67, 69].

<table>
<thead>
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<th></th>
<th>Dominant HER-2 profile %</th>
<th>Axillary lymph node involvement %</th>
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</thead>
<tbody>
<tr>
<td>Metaplastic</td>
<td>0–8</td>
<td>20 [64, 65]</td>
</tr>
<tr>
<td>Lipid rich</td>
<td>71</td>
<td>80 [66]</td>
</tr>
</tbody>
</table>

**Table 4.** Poor prognosis typically ER-negative tumors

**lipid-rich carcinoma**

**definition and epidemiology.** This is defined as a tumor in which ~90% of its neoplastic cells contain abundant cytoplasmic neutral lipids. Usually, it has very high-grade nuclear features and poorly differentiated growth pattern. The tumor accounts for 1%–2% of all breast cancer with 84% of reported patients presenting at age ≤50. In one series, 80% were diagnosed with involved axillary lymph nodes and most had more than three positive lymph nodes. In total, 71% (35 of 49) were diagnosed with stage III disease. Many pathologists do not consider this type as a separate entity.

**imaging.** Although the tumors consist of a large proportion of lipid, they present with a higher density than adjacent tissue at mammography.

**immunohistochemistry.** In the largest series (n = 49), 100% of the patients presented with ER-negative status. The vast majority (90%) were PgR negative as well. Her-2 overexpression was found in 71.4% of this kind of neoplasm, which was much higher than the 20% expected in the general invasive breast carcinoma population. High Ki-67 proliferation activity was found in 55% of the cases.

**prognosis.** The 2- and 5-year OS rates were 64.6% and 33.2%, respectively, with a median OS of 35 months. The only independent factor to predict survival was positive lymph nodes [66]. In an earlier report, 38.5% of patients died in the first year following mastectomy [73].

**‘unclassified’ due to lack of sufficient information**

**glycogen-rich clear-cell carcinoma of the breast**

**definition and epidemiology.** This is defined as carcinoma in which >90% of the neoplastic cells have abundant clear cytoplasm containing glycogen [1]. The incidence is 1.4%–3% of all breast cancers, presenting at a median age of 57. There is debate regarding this tumor’s behavior as some small series report high axillary lymph nodal rate involvement of more than 50% [53], whereas others report a much lower rate—35% (n = 20) [74].

**imaging.** There is not enough available data.

**immunohistochemistry.** In a series of 20 patients, 35% and 30% were positive to ER and PgR, respectively. In total, 20% presented with HER-2-positive status.

**prognosis.** Fewer than 100 cases have been reported; thus, it is difficult to draw definitive conclusions. Most authors have found that this tumor has a poor prognosis but there is no direct comparison to IDC-NOS based on stage [74, 75].

**oncocytic carcinoma (malignant oncocytoma)**

**definition.** The WHO classification requires >70% of the cells to be oncocytic ones; however, only very few case reports are published. Thus, we have found that no significant conclusion can be drawn.
sebaceous carcinoma

definition and epidemiology. This carcinoma is characterized by a lobular or nested growth pattern of tumor cells variably admixed with those displaying sebaceous differentiation. To our knowledge, only seven cases have been reported in the literature with ages ranging from 43 to 83 years. Sebaceous tumor may precede internal malignancies and a genetic consultation to rule out Muir–Torre Syndrome should be considered. A case with involved lymph node at presentation was reported [76].

immunohistochemistry. The hormone receptor status is typically positive; however, two cases were reported to be negative. No HER-2 overexpression was detected. In three analyzed cases, the percentage of Ki-67-positive tumor cells was relatively high and ranged from 16% to 38% [77].

prognosis. Sebaceous carcinoma (SC) is generally felt to have a worse prognosis than other cutaneous carcinomas. Due to the only scant published data, it is difficult to compare it with the breast IDC-NOS. SC that had metastasized to the bone and skin was reported. The case may imply on its aggressive potential [77, 78].

treatment data from the literature

These epithelial tumors are far too rare to have been studied with specific randomized clinical trials to determine the optimal surgical, radiation, chemotherapeutic or endocrine treatment. Although occasionally these rare tumor types have been included in large trials, the numbers are too small to draw any conclusions regarding their response to treatment. In most situations, they have been treated with standard therapy as there are no data to indicate special protocols.

Surgery is the first step of treatment of most of the early breast cancers. The standard of care is lumpectomy/ mastectomy with sentinel node biopsy (SNB). Many of the special types such as tubular, cribriform, medullary and mucinous have a low risk for regional involved lymph nodes but without more data, it is not clear whether SNB can be safely omitted.

Adjuvant radiation therapy has shown its benefit in breast cancer not only as a local control procedure but also as a treatment to prolong survival. ‘Favorable tumors’ tend to have lower rate of local and distant recurrences. When comparing IDC-NOS to medullary, tubular and mucinous types, no statistically significant differences were found in the local-regional failure rate among the four groups. In total, 31% of TCs and up to 37.5% of ACCs that had been treated with excision only developed local recurrence [33, 47, 79].

The significant parameters were still the traditional ones: age, margins, lymphovascular invasion and extensive DCIS [13, 39, 80].

Baker has stated that pure TC <1 cm in size could be treated by excision only [81]. However, the NSABP B-20 trial that had randomly assigned patients with small IDC tumors to yes/no adjuvant radiation could not find any subgroup which did not benefit from radiation therapy [82]. The seccrory type which is typically diagnosed in young girls represents a possible exception since there is a strong effort to preserve the breast bud without jeopardizing local control and to avoid rib, lung and other tissue damage. Thus, radiation may be omitted according to some experts but again, there is only scanty data.

As we cannot create systemic treatment algorithms using randomized trials with level one evidence due to the rarity of all these tumors, can we use small case reports? Diab et al. found that axillary node involvement was a poor prognostic feature in mucinous carcinomas but not in TCs. Their conclusion was that systemic adjuvant therapy and node dissection may be avoided in many patients with TC [13]. This conclusion is in accordance with the recent knowledge regarding the lack of sensitivity of luminal A breast cancers to chemotherapy and the role of endocrine treatments [83, 84]. However, further data are required before completely changing our guidelines for these tumors.

ACC as a histological definition appears to have both prognostic and predictive significance by some authors as there are concerns regarding the sensitivity of this subtype to chemotherapy based mainly on the documented low response rate in the head and neck adenoid cystic literature. There are data that this tumor has some response to chemotherapy drugs such as anthracyclines and 5-fluorouracil as well as more modern agents such as paclitaxel [85, 86]. Large series, however, are not available.

Recently, there has been interest in the platinum agents and they have been incorporated into the arsenal of treatment of the triple-negative or basal subtypes. Several studies had shown activity of these agents in the metastatic and neoadjuvant treatment but larger studies are still pending. Knowing that phase III trial results for these rare types will not be forthcoming, can we make a leap and recommend platinum agent in the adjuvant setting for certain rare triple-negative subtypes such as metaplastic or the aggressive small-cell tumors? There is certainly rationale in administering adjuvant cisplatin regimen in SCC breast cancer. This tumor has an aggressive course and there are data showing a high rate of response in small-cell lung and extrapulmonary metastatic disease. If NE breast cancers are just another extrapulmonary site of small-cell tumors, they may be treated in a similar fashion but we do need to remember that for the adjuvant breast cancer setting, this is not an evidence-based recommendation. For other types of these tumors, further studies are necessary before treatment algorithms can be created.

summary

Rare epithelial breast cancers are a heterogeneous group of malignancies with different behaviors and prognoses. Although histopathology has been our standard, there is now the question of whether it is time to apply new technologies such as microarrays and deep gene analysis to further understand these rare tumors. Are they all really unique subtypes or not? Can they be classified according to their molecular or genetic features? Are the older histological subtypes of value in understanding the behavior of these rare tumors and are they really classifying specific tumors or not?

We have tried to classify these tumors with the data we have currently on ER status and outcome. These broad groups of
estrogen-positive good outcome or poor outcome or similar estrogen-negative groups may be helpful in terms of conceptualizing where we are going but need further assessment. As well, the poor prognosis of some of these subtypes reflects the need for a better adjuvant treatment and an understanding of these specific groups based on both their histological appearance and their molecular staining.

We are proposing and organizing a consortium of investigators from around the world to gather a sizable number of these rare tumor types, assess the tumors centrally by modern array technology and try to group these with outcome and treatment data. This has been established for the common tumors and we have many leads as to their subclassification but a further analysis of these rare tumors is also needed. This exercise may provide the necessary information to begin to further understand the behavior of these tumors and to begin to classify them according to their relevant features. Subsequently, there may be a role for trials using a contemporary classification to look at uniform treatment modalities and begin to establish treatment algorithms and guidelines. Until such time, we believe broad classifications into the good and bad prognostic groups may be helpful for the clinician faced with a patient with one of these tumors and only anecdotal case histories for reference.

acknowledgement
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