Review Article

Rare epithelial breast cancer: surgery and adjuvant therapy

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Abstract: Breast cancer is a heterogenous disease, exhibiting a wide range of morphological phenotypes shaping its prognosis and clinical course. However, optimal management of rarer breast cancer subtypes is often undefined and controversial in literature due to the lack of large studies and randomised trials. This review aims to discuss the treatment of 13 rare epithelial subtypes, focussing on surgery and adjuvant therapies.

Keywords: Epithelial breast cancer; surgery; adjuvant therapy; optimal management

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Introduction

Being one of the biggest causes of cancer mortality worldwide, breast cancers exhibit a wide range of morphological phenotypes with invasive ductal cancer (IDC) being the commonest, followed by invasive lobular carcinoma (ILC) representing 70–80% and 15% of all breast cancer cases respectively. IDC and ILC have been extensively studied in randomized control trials to determine their morphology and optimal treatment leading to a well-defined therapeutic approach (1).

The standard management of such breast tumours is primarily surgical removal of the tumour, ranging from mastectomy to breast conserving surgery (BCS). Patients receiving BCS also typically receive adjuvant radiotherapy unless contraindicated. In order to determine, axillary node status, breast cancer patients undergo sentinel lymph node biopsy (SLNB), and if positive/high axillary involvement (≥2 lymph nodes positive) axillary lymph node dissection (ALND) is indicated.

However, rarer tumours which have been defined by specific clinical or prognostic characteristics lack the consensus in the treatment approach found in more common cancers. This review aims to outline the treatment, particularly the surgical and adjuvant therapies of the rarer forms of breast cancers with a focus on epithelial breast tumours.

Pure tubular carcinoma

Pure tubular carcinoma is a variant of the more common IDC, it is well differentiated and has an orderly tubule formation. Associated with a good prognosis, pure tubular carcinoma is almost always oestrogen (ER) and progesterone (PR) receptor positive and may occasionally be HER-2 receptor positive (2)

Tubular carcinomas are characteristically small, can be impalpable and are often detected on screening by mammography (3). Traditionally, tubular carcinomas were managed by mastectomy with some studies indicating the favourable prognosis after the procedure. However, the necessity of mastectomy was brought into question after further studies indicated that BCS, with or without adjuvant therapies would be the more suitable and effective approach for this type of tumour. Anan *et al.* indicated that the features of tubular carcinoma reduced the likelihood

of local recurrence post breast-conserving therapy. This included the size of the tumour. The typically small tumour is an advantage for ensuring a negative margin at time of resection (4). Furthermore, none of the 17 cases in the study showed extensive intraductal spread or lymphatic tumour emboli which significantly reduces the likelihood of positive surgical margins at time of resection (3). These findings are also supported in a study by Holland *et al.* which demonstrated that tumours with intraductal extension had a 30% greater chance of having residual carcinoma after surgery (5). These factors, alongside the insignificant difference found between the prognosis of patients treated by mastectomy and local excision indicates the effectiveness of BCS (6,7).

Similarly to more common breast carcinomas, BCS is an effective way of managing tubular carcinomas. However, the impact of adjuvant therapy is not as well studied in tubular carcinomas and therefore may not be indicated as is the case with other tumour types following BCS.

Despite the low rate of axillary metastases (ranging from 5–20%) in tubular carcinomas, the debate around axillary management is one that continues (3,8), lymph node positivity has often been reported as the most important prognostic factor in breast cancer prognosis (3).

SNB is a standard practice in most patients with breast carcinomas. However, many authors recommend sentinel node biopsy in patients with primary tubular carcinoma of a size greater than 10 mm. Cabral *et al.* demonstrated the correlation between tumour size and node positivity (9). Tumours greater than 15 mm were more likely to be associated with node positivity, this was contradicted by Sullivan *et al.* retrospective analysis of 73 cases in which only one patient had positive lymph nodes with a tumour size of 7 mm.

Even if axillary nodes were positive in a patient, the necessity of axillary node dissection remains questionable with studies such as Winchester *et al.* and Sullivan *et al.* finding no correlation between nodal metastases and disease-free survival in patients with tubular carcinoma (8,10). Sullivan *et al.* reported that out of 27 patients who underwent ALND patients 5 were axillary node positive and none of them had a recurrence of the tumour. Additionally, Lea *et al.* found that out of 146 patients the 4 cases of recurrent tumour were all node negative indicating that perhaps lymph node positivity does not have the suggested prognostic value for patients with tubular carcinoma (3). This suggests that despite SNB being common practice in most breast cancer patients, the little effect that node positivity may have on prognosis means that pure tubular carcinoma may not necessitate SNB or ALND.

Tubular carcinoma has also been treated by various types of adjuvant therapies, ranging from radiotherapy to systemic chemotherapy and endocrine therapy. The benefits of adjuvant radiotherapy post-surgery in females younger than 65 years has been described in the literature. Li *et al.* recommend adjuvant radiotherapy based on a statistically significant 3% improvement in overall survival in patients who received adjuvant radiotherapy in comparison to the cohort who have not (11). The benefit of adjuvant radiotherapy must be weighed against the excellent prognosis of tubular carcinoma and the risks of the therapy itself such as radiation induced subacute pneumonitis and long-term cardiac toxicities. Furthermore, Sullivan *et al.* observed that the 3 patients who presented with local recurrence had all been treated by lumpectomy followed by radiotherapy, however, the review indicated that recurrence is more likely if adjuvant radiotherapy is omitted. Although adjuvant radiotherapy has proven to be useful, decreased incidence of local failure may indicate that less aggressive radiotherapy techniques such as partial breast irradiation should be considered.

Tubular carcinomas are often found to be hormone receptor positive making hormonal therapy a potential suitable adjuvant therapy. The national institute of health recommends treating all women with hormone receptor positive breast tumours with endocrine therapy. However, Sullivan *et al.* found that both chemotherapy and hormonal therapy were not linked to a reduction in local recurrence. Poirier *et al.* also found that chemotherapy seemed to have no impact on patient survival (12). This was supported by previous studies (3,13). One study, however, still suggest that chemotherapy is of value in patients with tubular carcinoma (14).

Invasive cribriform carcinoma (ICC)

ICC, considered a low-grade carcinoma, is characterised by a predominantly cribriform pattern of its invasive component. ICC typically expresses oestrogen and progesterone receptors, but rarely expresses HER-2.

Surgery is the primary treatment for ICC although the extent of surgery is not discussed in literature (15).

In case report Zhang *et al.* demonstrated the potential for ICC to develop into stage T4 if left untreated and metastasise to the bone. In that case the patient was treated with neoadjuvant chemotherapy due the large

size of mass and two enlarged lymph nodes, followed surgery and endocrine therapy. This was followed up by thoracic radiotherapy due to the possibility of bone mass metastasis (16). The study reported benefit in neoadjuvant chemotherapy as the tumour and axillary nodes both reduced in size. However, the effect that postoperative local and systemic therapies have cannot be discounted.

Furthermore, recent studies have questioned the suitability of chemotherapy for treating ICC (17-19). Colleoni *et al.* suggested that luminal tumours with favourable histotype may not require any adjuvant therapy or just endocrine therapy (20). However, since recurrence is possible high-risk patients are recommended chemotherapy and radiotherapy.

Adenoid cystic carcinoma

Adenoid cystic carcinomas are very rare tumours that make up less than 0.1% of all breast cancers (21). They can be histologically classified as cribriform, tubular or solid and are typically hormone receptor and HER-2 negative (2,21).

Due to the rarity of adenoid cystic carcinoma (ACC), no definitive locoregional treatment guidance, encompassing both surgical and adjuvant therapies have been outlined to date. Mastectomy and later modified radical mastectomy were the most common surgical procedures for ACC of the breast in the past. Given the very few recurrences that were seen after mastectomy, it was recommended by authors as the standard treatment of ACC of the breast particularly in patients with high-grade tumours with or without axillary node dissection (22,23).

Local excisions of ACCs alone have been performed in the past and associated with high rates of recurrence. Leeming *et al.* demonstrated this point after 37.5% (9 out of 24) of patients in the study had local recurrence of cancer after receiving local excision without adjuvant radiotherapy (24). This was also supported by the findings of Sumpio *et al.* who found that 6 out of the 8 patients who had local recurrence of cancer had undergone local excision (25). The role of adjuvant radiotherapy alongside BCS must be assessed before BCS as a management of ACC is dismissed.

In many of these cases however, no information was given regarding the margins' status. Kleer *et al.* found that more than 50% of patients with recurrence were found to have positive margins and followed with a recommendation of treating ACCs by wide tumour resection with clear margins (26).

More recent studies have demonstrated that good local control can be achieved by lumpectomy and adjuvant radiotherapy (27), with Arpino *et al.* reporting that of all cases treated by lumpectomy followed by radiotherapy (n=5), no recurrence was described. This was further supported by Coates *et al.* study, with one of the greatest numbers of ACC cases, which indicated that RT following local surgical resection significantly improved cause specific and overall survival when compared to lumpectomy alone (28). This demonstrates that the management of ACCs surgically closely follows that of more common tumour types. However, in order to optimize treatment for ACC tumours, further investigation into the radiosensitivity of ACCs of the breast may be required.

ACCs of the breast unlike ACCS of the head and neck do not characteristically metastasise to axillary lymph nodes. Only 4 cases of lymph node metastases were found in the Arpino *et al.* reviewed 182 patients who undergone axillary dissection (27). This was further emphasised by a study of 30 patients 10 of whom had axillary node dissection and 2 sentinel node biopsies which were all negative, with the authors concluding that lymphadenectomy is therefore unnecessary in this type of tumour (28,29). However, the effect of node positivity on prognosis has not been fully explored thus adhering to common practice in undergoing SNB followed by ALND (if axillary burden is high) is the safer option.

The use of chemotherapy is uncommon [with only 11% of patients receiving adjuvant chemotherapy (30)] and not yet standardized for ACCs although conventional chemotherapy regimens are used as first-line therapy in patients with advanced tumour stage (31). Laurie *et al.* recommended the use of mitoxantrone, epirubicin or vinorelbine in treatment of ACC after assessing different regimens based on their outcomes (32). Other studies have reported that the effects of other commonly administered chemotherapy agents such as cisplatin, paclitaxel and gemcitabine were often insignificant (32,33).

Hormonal therapy is not often used due to the tumour's typical ACC negative hormone receptors. However, it may be indicated in the rare cases where there is ER/PR receptor positivity.

Over expression of MYB-NFIB fusion gene in ACCs may have a role in the development of targeted therapy for ACCs which may transform the management of this rare carcinoma (34,35).

Acinic cell carcinoma

Acinic cell carcinoma is a tumour that typically arises in the

salivary gland. Characterised by widespread acinar cell-like differentiation, acinic cell carcinomas are typically ER, PR and HER-2 negative (1). With only 39 cases being reported thus far the rarity of acinic cell carcinoma, like other rare epithelial breast cancer has meant that no consensus on optimum treatment has been reached (36). Additionally, since the first case of ACC reported in 1996, different surgical approaches to managing ACC had been taken without any comparison of surgical approaches and prognosis.

Despite commonly being typically a triple negative cancer, acinic cell carcinomas are usually classified as low-grade tumours, often with a good prognosis (2,37). This, however, was contradicted by Coyne *et al.* who reports cases of grade 2 and grade 3 tumours and worsening prognosis, particularly when associated with additional poor prognostic features such as vascular invasion (38). Damiani *et al.* also described cases of patients with ACC of the breast associated with a poor prognosis. Out of 6 the patients described (all treated surgically) 2 were found to have lymph node metastases suggesting a more aggressive method of treatment and in conjunction with common practice adjuvant therapy is required in treating some patients with acinic cell carcinoma (39).

Surgical approaches described in a review by Limite *et al.* included both modified radical mastectomy (n=16) and BCS (n=15). Seven patients received neoadjuvant chemotherapy, six received radiation therapy (37). Locoregional reoccurrence was reported in one patient who did not receive any adjuvant therapy following lumpectomy and metastasis was found in four patients following surgery with neoadjuvant/adjuvant chemotherapy and radiotherapy. The necessity of adjuvant therapy was therefore put into question. Unlike the standard treatment of more common breast tumours, Limite *et al.* recommended BCS with no adjuvant therapy as a suitable way of treating acinic cell carcinomas, although this must be further explored.

However, the necessity of adjuvant radiotherapy and chemotherapy must therefore be discussed on a case by case basis. Due to the small number of cases reported no valid conclusion regarding the optimal management of acinic cell carcinoma can be taken. Further research and case reports are required for a consensus on treatment of acinic cell carcinoma to be reached.

Apocrine carcinoma

Apocrine carcinomas are typically androgen receptor positive but ER, PR negative tumours that make up from 0.3–4% of all breast cancer patients (40,41). Furthermore, approximately 50% of apocrine carcinomas over-express HER-2 (42,43). They are characterised by typical apocrine features such as abundant eosinophilic granular cytoplasm and multiple prominent nuclei (43). They often have a favourable prognosis (42).

Like most breast carcinomas, primary treatment of apocrine carcinoma is surgery. However, the extent of surgery which is indicated in patients with apocrine carcinoma is unknown. Some studies have shown that positive rates of axillary nodal metastasis (ANM) and lymphatic invasion in patients could reach up to 27% and 18% respectively (44). Given that ANM and lymphatic invasion were associated with worse prognosis inpatients with intraductal carcinoma, it vital to consider sentinel node biopsy (SNB) in patients with apocrine carcinoma. Even more perhaps than more common tumours.

The necessity of neoadjuvant chemotherapy prior to surgery has been put into question due to the limited benefit it has on the prognosis of apocrine carcinomas (45). However, Guarneri *et al.* reported that HER-2 positive tumours were likely to have better response to chemotherapy, suggesting that perhaps only HER-2 negative apocrine tumours would not benefit from neoadjuvant chemotherapy (46). Adjuvant chemotherapy was also recommended in patients with triple negative apocrine tumours (41).

It has been suggested that apocrine carcinomas may be a good candidate for adjuvant hormone therapy targeted against AR receptor positive tumours (2). EGFR overexpression has also been reported. This can potentially be exploited in generating a targeted therapy for apocrine carcinoma (42).

Unfortunately, due to the rarity if the disease, no treatment algorithm has been recommended, management is often dictated by cancer stage and treated as invasive ductal carcinoma. Further research and randomised control trials are required to generate the optimal treatment for this type of carcinoma.

Mucinous carcinoma

Accounting for 1–4% of all breast malignancies, Mucinous carcinoma is a rare epithelial tumour of the breast characterised by the production of mucin both extracellular and intracellular (47). Mucinous carcinomas can be either pure (90%) or mixed (50–90%) (48). The tumours are typically oestrogen and progesterone receptor positive and HER-2 negative, contributing to a good prognosis (49).

A review of 65 cases of mucinous carcinoma showed that modified radical mastectomy was typically used as the preferred surgical treatment of the past with an increasing number of patients being managed by BCS more recently. The review found that extent of surgery did not influence survival. Twenty-five patients in the study also received adjuvant therapy following BCS, however it was difficult to assess its effect on management as it was often given sporadically (50). Anan *et al.* concluded that cases of pure mucinous carcinomas including large tumours up to 5 cm in diameter (except tumours that invade local skin) are suitable candidates for BCS (51). This is partly due to the low incidence of extensive intraductal spread in pure mucinous tumours. Cases where spread has occurred often tend to be of the non-comedo type which behaves less aggressively than comedo types, making this particular carcinoma type ideal for BCS.

Anan *et al.* also discussed the need for axillary node dissection. The incidence of ALNM was particularly low in pure mucinous carcinoma with lymphatic invasion present in only 4% of cases and up to 15% in other studies (52). However, some correlation seems to exist between the size of tumour and lymph node involvement. The study found that all tumours less than 3 cm showed no lymph node involvement which suggests that small pure mucinous tumours an ideal candidate for lumpectomy without axillary node dissection. This was confirmed by studies reporting the unlikely nature of T1 tumours developing lymph node metastases (53,54). However, similarly to more common breast tumour types, lymph node involvement in Mucinous tumours was the largest risk factor for poor prognosis therefore SLNB should be considered (49).

Studies have suggested that adjuvant endocrine therapy is indicated and likely to be an effective treatment for mucinous tumours, nearly all of which are oestrogen and progesterone receptor positive (55,56). With some even reporting dramatic effects on locally advanced mucinous carcinoma even after chemotherapy (56). Nakagawa *et al.* suggested that optimal management for inflammatory carcinoma should encompass a combination of therapies (56). However, a study which compared primary endocrine treatment to multimodal treatment with neoadjuvant radiotherapy found no significant difference between the two groups in terms of five-year specific survival (57). Other studies have also reported no significant difference between chemotherapy and endocrine therapy in terms of survival benefit and overall response. Suggesting either treatment modality is effective (58,59). The need for adjuvant chemotherapy/hormonal therapy was discussed in a paper by Bae *et al.* which found that secondary to nodal status, adjuvant chemotherapy/hormonal therapy use was a significant prognostic factor (60). Despite this, some authors have suggested that systemic adjuvant therapy can be avoided in patients with mucinous carcinoma. One case of mucinous carcinoma reported by Yamaguchi *et al.* found poor clinical response to neoadjuvant chemotherapy. However, a good pathological response was reported (61).

Medullary carcinoma

Medullary carcinomas are characterised a syncytial growth pattern, a large vesicular nuclei, prominent nucleoli and lymphocytic infiltration throughout the tumour and a broad pushing margin (62). Atypical carcinomas are a subtype of medullary carcinomas where the tumour has less lymphocytic infiltrate. This tumour type is often HER2 and ER negative and P53 positive (2).

Following standard breast tumour management guidelines, BCS, axillary staging and adjuvant radiotherapy is indicated in these patients. The efficacy of adjuvant chemotherapy however has not been properly explored. Forquet *et al.* suggested that adjuvant chemotherapy had no survival benefit whereas adjuvant radiotherapy did. This countered some contradiction from Dreyer *et al.*' study which found that triple negative carcinomas such as medullary carcinoma of the breast were at greater risk of relapse in younger patients who did not receive adjuvant chemotherapy or radiotherapy. The necessity of adjuvant therapy in the elderly however was questioned in that study (63). Some studies have indicated that despite the favourable prognosis that medullary carcinomas carry the rate of axillary node metastasis is still incredibly high with some studies such as Wong *et al.* reporting a 21% rate of axillary node metastasis. This suggests that ALND staging is essential (64).

Secretory breast carcinoma (SBC)

Accounting for less than 0.02% of all breast cancers, secretory breast carcinomas are incredibly rare. It is often reported to be a triple negative tumour, however a more recent study of 246 cases of secretory breast carcinoma has indicated that this may not be the case (65). It is often well differentiated and has been reported to affect younger individuals with mean occurrence in adults aged 40 (66). SBC tumours are also characterised by the presence of ETV6-NTRK3 gene fusion associated with translocation t(12:15). It is defined by WHO as a low-grade invasive

carcinoma with a solid, microcystic and tubular arrangement of cells that produce intracellular and extracellular secretory material (67).

Data comparing the efficacy of adjuvant treatment and different types of breast surgery is scant, however some studies have shown that clinicians tend to treat SBC in the same way that cases of Intra ductal carcinoma is treated. This is particularly in the use of BCS and hormone therapy (for hormone positive cases). Despite the increase in BCS used to treat SBC, case reports of chest wall recurrence after BCS may suggest that more invasive procedure with axillary sampling may be necessary (68).

The use of adjuvant chemotherapy tended to be much lower than in IDC however this perhaps is due to a greater proportion of grade I SBC cases in comparison to IDC. Some studies have also reported of poor response of SBC tumours to chemotherapy (69). Herz *et al.* case report found that all stages of chemotherapy was not effective at reducing the size of metastatic SBC. Chemotherapy was therefore not recommended without objective clinical response and sustained symptom relief that could not be achieved through other palliative treatments.

A study analysing the SEER database compared the overall survival and disease-free survival (DFS) between SBC cases treated with adjuvant radiotherapy with those who were not treated with radiotherapy. Although the sample size was too small to conduct any meaningful statistical analysis, there was an improved mean OS and DFS in those who received radiotherapy in comparison to those who did not (69). Adjuvant radiotherapy after BCS has been demonstrated to improve DFS and locoregional control in patients with local resection of invasive carcinoma (70). This suggests that SBCs can be managed in a similar manner to more common carcinomas of the breast.

Recently, a case of reoccurring SBC in a 14-year-old patient was successfully treated using pan-Trk inhibitor Larotrectinib with minimal toxicity. The response to treatment was reported to be almost immediate and complete (54). This was further validated by a recent phase 1 trial which also revealed responsiveness of NTRK fusion tumours, suggesting that Larotrectinib and other Trk inhibitors may have the potential to become the gold standard treatment for SBC expressing the ETV6-NTRK3 fusion.

Neuroendocrine tumours (NETs)

NETs make up approximately 0.1% of all breast tumours and have been defined by WHO [2003] as tumours that express neuroendocrine markers such as synaptophysin and chromogranin in more than 50% of cells (71-73). NETs tend to be hormone receptor positive and HER-2 negative (74). WHO's current classification differentiates between 3 subtypes of NETs: well differentiated NE, poorly differentiated NE/small cell carcinoma and invasive breast carcinoma with neuroendocrine differentiation (75). The categorisation of these groups is important given that treatment for each subtype may differ slightly although the differentiation into what type of NE tumour has no impact on prognosis (76).

As is the case with most breast tumours surgical resection is the recommended first-line (77), the extent of the resection however is not clear due to the rarity of cases. Mastectomy seemed to be the preferred surgical approach given that NETs have the potential to be aggressive at early stages of tumours, however, BCS is being used more frequently either with or without adjuvant therapy (77,78). Although BCS is recently becoming a more frequent choice, evidence supporting its use over mastectomies for NETs is lacking. Differentiating between primary and metastatic NETs is also incredibly important when considering which surgical approach. The latter is often treated by BCS as opposed to a mastectomy and axillary node dissection (79).

Studies regarding the impact of adjuvant radiotherapy on NETs is also lacking, Multiple studies have reported no change in survival after radiation therapy (72,80). On the other hand, Wei *et al.* in a retrospective study of 74 patients, reported that treatment with adjuvant radiotherapy and hormonal therapy may be beneficial in terms of outcome survival in comparison to ductal carcinoma, although this was not statistically significant, potentially due to the small sample size (81). Adjuvant radiotherapy should be considered as it is widely recommended for other types of invasive breast cancers. However, with the current small number of cases it is unclear whether NETs should be managed following guidelines of more common tumours, with adjuvant radiotherapy administered after BCS.

Adjuvant systemic therapy should be given after considering prognostic factors of the tumour, tumour size, histological grade and nodal metastases being the main factors in NETs as in other invasive carcinomas (72). Adjuvant chemotherapy is recommended in patients with high risk of relapse and adjuvant endocrine therapy is indicated in patients with hormone receptor positive tumours. Tumours with positive hormone receptors and high Ki67 expression may benefit from both adjuvant

chemotherapy and endocrine therapy given the poor prognostic role of proliferation index.

Multiple studies have described the effect that chemotherapy has on NETs with some suggesting that chemotherapy regimens used for invasive NETs can be used as adjuvant/neo-adjuvant chemotherapy (82). Small cell NETs tend to be treated using the same chemo-regimen as small cell lung carcinomas due similarities between the two types in terms of clinical, histological and morphological features (83,84). Oberg *et al.* suggested administering different types of chemotherapy according to a modified therapeutic algorithm used for gastrointestinal tumours which depends on the Ki67 index. Patients with Ki67 less than 15% were given anthracycline-based therapy and patients with Ki67 greater than 15% were given cisplatin/etoposide (85). However, given the lack of data on the effect of etoposide and platinum compounds on NETs of the breast some have recommended treating these tumours in the same manner as ductal breast carcinomas, preferentially using anthracyclines or Taxanes (86). However, Roininen *et al.* did not find Ki-67 to be a predictor of survival which suggests that altering chemotherapy based on tumour marker KI-67 is not the most suitable approach (87). Wei *et al.* found that the use of adjuvant chemotherapy was in fact not associated with a better prognosis in comparison to invasive ductal carcinoma. A combination of chemotherapy, radiotherapy and hormonal therapy also seemed to have no added prognostic value (80,87).

The use of adjuvant endocrine therapy is generally thought to improve survival in patients with hormone receptor positive tumours as occurs in many cases of NETs (81,88). However, evidence of efficacy is currently anecdotal, and the evaluation of further cases and clinical trials of NETs is necessary for the development of an optimal treatment strategy.

Metaplastic breast carcinoma (MBC)

Metaplastic carcinomas accounts for approximately 1% of all breast carcinomas and is associated with a poor prognosis despite low nodal involvement and aggressive local and systemic therapy (89). This tumour is characterised by the presence of two or more cellular types, typically epithelial and mesenchymal components. Metaplastic carcinoma is categorised into different subtypes according to the WHO's most recent classification. These are: (I) metaplastic carcinoma of no special type, (II) low-grade adenosquamous carcinoma, (III) fibromatosis-like carcinoma, (IV) squamous cell carcinoma, (V) spindle cell carcinoma, (VI) metaplastic carcinoma with mesenchymal differentiation, (VII) mixed metaplastic carcinoma, (VIII) myoepithelial carcinoma (75).

Treatment of MBC at both early and locally advanced stages encompasses, surgery, radiotherapy, hormonal therapy and chemotherapy. Given the tumour's rapid growth and large size either a simple or modified mastectomy is often the treatment of choice. BCS can be used depending on the case and with a wide surgical margin, >3 cm (90). Dave *et al.* found that BCS (followed by adjuvant radiotherapy) have the same survival benefits as a mastectomy (91). This was also supported by Pezzi *et al.* and Tseng and Martinez who found no significant difference in overall survival or disease-free survival between patients who had undergone BCS in comparison to those who had a mastectomy (92,93). Despite the rate of growth of tumour axillary lymph node metastases is low and no correlation seems to exist between ALN metastases and clinical outcome. This puts the need for ALND as a primary investigation of lymph node positivity into question and could perhaps be replaced by SLNB (94,95). Despite the seemingly more aggressive clinical course of MBC, studies so far have shown that the surgical management of MBCs can follow that of more common breast carcinomas.

The role of adjuvant radiotherapy is not extensively described in the literature. Dave *et al.* reported that out of 3 patients who did not receive adjuvant radiotherapy after BCS, 2 presented with local recurrence (91). Tseng and Martinez analysis of the Surveillance, Epidemiology and End Results found that adjuvant radiotherapy had an impact on survival regardless of surgery type, although the benefits of adjuvant radiotherapy is much greater following BCS than mastectomy (92). It is therefore, advised to follow up BCS with adjuvant radiotherapy to reduce the risk of reoccurrence. However, adjuvant radiotherapy had no survival benefit in patients with tumours <5 cm or <4 metastatic ALN who are undergoing a mastectomy (90). Other studies have also reported that MBCs were in fact irresponsive to adjuvant radiotherapy (96). This demonstrates a need for clear guidelines for the use of radiotherapy tailored for MBC.

The efficacy of adjuvant/neoadjuvant chemotherapy remains controversial in treating MBCs. MBCs are reported to be resistant to chemotherapy with little reported benefit in comparison to other breast tumours (97). 90% of patients in Chen *et al.*'s retrospective study experienced disease progression despite neoadjuvant chemotherapy. Taxane-based regimens have proven to be the most effective as

a neoadjuvant therapy in comparison to others although outcomes remain poor (98). Despite that, adjuvant chemotherapy seems to improve prognosis in patients especially with those in early-stage disease (T1 and T2). Cimino-Mathews *et al.* demonstrated that MBS treated with adjuvant chemotherapy had improved OS compared to those who did not receive it. A review of 285 cases also showed improved cancer specific survival in patients who had received adjuvant chemotherapy (99).

MBCs are typically hormone and HER-2 receptor negative, with one study reporting 92.2% negativity, making the efficacy of targeted therapies such as Trastuzumab unlikely and an unsuitable treatment option (96).

Hormonal therapy also seems to be ineffective when treating most MBCs as they are often hormone receptor negative (100). Even in cases where hormonal therapy had been appropriately administered, results were poor, further reaffirming the poorer prognosis of MBCs in comparison to other tumours, including triple negative IDCs (101).

Papillary carcinoma of the breast

Papillary carcinomas (PC) are tumours characterised by proliferation of malignant epithelium with fibrovascular stalks (102). PC can be categorized into subtypes: Encapsulated/intracystic PC, solid PC, intraductal PC, invasive PC and papillary ductal carcinoma *in situ* (103,104). PC are almost always oestrogen and progesterone receptor positive and HER-2 is often found to be negative (105).

Both diagnosis and clinical management of PC is controversial in literature despite the tumour's rarity making up 0.5–1% of all breast carcinomas (103). Clear diagnostic guidelines are required particularly if it indicates different treatments. Encapsulated or Solid PCs, if reported as an invasive tumour, could require systemic adjuvant therapy (106).

Treatment of PC varied in the literature from surgery alone to trimodal therapy encompassing surgery, adjuvant radiotherapy and chemotherapy (107). Unfortunately, studies comparing different treatment modalities and their outcomes is lacking.

In a retrospective SEER report, invasive PC were found to be mainly treated by breast-conserving surgery over other surgical methods, as it is associated with a more favourable prognosis in comparison to IDCs in terms of disease-free survival. The study found that invasive papillary tumours were typically smaller in size, lower grade and had reduced lymph node involvement which explains the reason BCS was the preferred option (108). The excellent prognosis also suggests that ALND may not be necessary rather SNB should be first line. These observations were also reported in previous studies (108,109). In a series of 40 cases of three subtypes of PC (Papillary in situ, Invasive PC, Papillary DICS), Solorzano *et al.* found that prognosis did not differ between the three subtypes nor by the type of surgery (Mastectomy or segmental mastectomy) or administration of radiation therapy (110). Fayanju *et al.* in a series of 45 patients found that no patient with pure Intracystic PC had failed BCS suggesting that there is no need for mastectomy in such patients.

Regarding the use of adjuvant radiotherapy and/or endocrine therapy, Fayanju *et al.* concluded that they should be considered in patients with pure intracystic PC who are under the age of 50 years although there is no clear evidence for its use specifically in PC tumours (111). Mogal *et al.* analysed the SEER database and concluded that there is in fact improved survival for patients receiving adjuvant radiotherapy following BCS in intracystic PC (112). Axillary node and distant metastases have been reported (in intracystic and solid PC) which may indicate the use of systemic adjuvant therapy; however, incidence of such events is extremely rare that such treatment would not be warranted (112,113). Hormonal therapy may be required in cases where PC is recurrent (114,115).

A randomized control trial is necessary to assess the impact of adjuvant radiation and endocrine therapies on prognosis of PCs to determine its optimal treatment regimen.

Pleomorphic variant of lobular carcinoma (PLC)

PLC, also known as polymorphous carcinoma, is a rare variant of ILC that accounts for less than 1% of all breast carcinomas and less than 5% of lobular carcinomas (2,116). PLCs are characterised by proliferation of pleomorphic and giant tumour cells making up >50% of tumour cells (116). They are often ER, PR negative, HER-2 positive and have a higher Ki67 index in comparison with typical ILC, immunohistochemical staining for E-cadherin can aid diagnosis of PLC (116). PLCs are often reported to be aggressive although Nguyen *et al.* reported not all PLCs carry a poor prognosis which is in fact associated with higher mitotic rate, larger tumour size and the presence of spindle cell metaplastic component (117).

Studies exploring outcomes of different treatments on PLCs are scarce therefore patients are often treated similarly to patients with high-grade tumours (118). Given its potentially poor prognosis, some authors have suggested that PLCs should be treated more aggressively than ILC (119).

Use of adjuvant chemotherapy may be indicated due to reports of distant metastases in patients with PLC (same reference as sentence before it).

Targeted therapy using trastuzumab, may be suitable in some patients with PLC given that the tumour expresses HER-2 (120). Mahtani and Vogel reported good response to trastuzumab in 4 patients (121), although this was not found to be the case by others (122).

Primary squamous cell carcinoma (PSCC)

PSCC is a rare tumour of the breast that accounts for up to 0.2% of all invasive breast carcinoma (123,124). PSCC tumours are characterised by malignant squamous cells that make up more than 90% of the tumour. They are often hormone receptor and HER-2 negative and are described as an aggressive type of metaplastic carcinoma of the breast associated with poor prognosis (124-126).

The poor prognosis and invasiveness associated with PSCC often indicated mastectomy as opposed to BCS in many cases, with studies reporting favourably on the use of mastectomy over BCS. Furthermore, PSCC are often larger in size and this may explain the lower rate of BCS use than in other tumour types (127). Despite that, Zhang *et al.* reported that none of the five patients who had undergone BCS had local regional recurrences. They also suggested that lumpectomies in elderly patients with co-morbidities is a suitable and safe option (128).

The efficacy of adjuvant radiotherapy is somewhat controversial in the literature. Although it may seem necessary to treat patients with adjuvant radiotherapy given the aggressive nature of the tumour, some studies have reported locoregional relapse occurring within irradiated areas indicating that PSCC may be radioresistant (125). Other studies have found that adjuvant radiotherapy following BCS simply provided no significant benefit on OS in patients with PSCC, deviating away from the standard management of more common breast tumours although that may be due to the small sample size (129). However, Wu *et al.* found that adjuvant radiotherapy had a significant association with improved overall survival in patients with PSCC particularly Stage II tumour and PN0 (130).

Regarding the efficacy of chemotherapy, studies have reported limited response of PSCCs to some chemotherapy regimens (125). Hennessy *et al.* found that none of five patients treated with neoadjuvant chemotherapy responded to treatment, this trend was also reported by Zhang *et al.* and others (128,129). However, two of three patients treated with platinum-based chemotherapy in an adjuvant setting were found to be relapse free (125). A case report of a patient with PSCC treated with neoadjuvant cisplatin/fluorouracil found that there was no residual PSCC or ALN metastases (131). Another study reported good response in 4 patients who receive cisplatin-based adjuvant chemotherapy regimens (129). This suggests that platinum-based regimens may be more suitable and have some effect in treating PSCC.

Given the fact that most PSCC are hormone receptor and HER-2 negative, hormone therapy is unlikely to be effective (124). Some authors recommended the use of endocrine therapy in hormone receptor positive PSCC, with Zhu and Chen finding a significantly improved overall survival in patients who received hormonal therapy (127). Despite hormone and HER-2 negativity in PSCC tumours, studies have reported overexpression of EGFR (132,133). This can be exploited by using anti-EGFR agents which according to some studies, if coupled with cisplatin-based therapy could radiosensitise squamous carcinoma cells (134,135). These findings have not been replicated in squamous carcinoma of the breast, however. Thus, further research is required.

Conclusions

There are many different types of rare epithelial breast cancers each with its unique histopathology and clinical course. The rarity of such cancers makes it difficult to reach adequate conclusions about their optimal management. Some studies indicate that some rare epithelial tumours would benefit from standard treatment of more common breast carcinomas, with BCS followed by adjuvant radiotherapy and SLNB. Other types are also managed by surgery although necessity of adjuvant radiotherapy and even SLNB are questioned. More cases of such rare epithelial breast carcinomas are required alongside randomised control trials to identify optimal therapy for these cancer types.

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References

1. Yerushalmi R, Hayes MM, Gelmon KA. Breast carcinoma--rare types: review of the literature. Ann Oncol 2009;20:1763-70.
2. Acevedo C, Amaya C, Lopez-Guerra JL. Rare breast tumors: Review of the literature. Rep Pract Oncol Radiother 2014;19:267-74.
3. Lea V, Gluch L, Kennedy CW, et al. Tubular carcinoma of the breast: axillary involvement and prognostic factors. ANZ J Surg 2015;85:448-51.
4. Anan K, Mitsuyama S, Tamae K, et al. Tubular carcinoma of the breast: a histologic subtype indicative of breast-conserving therapy. Surg Today 2000;30:1057-61.
5. Holland R, Connolly JL, Gelman R, et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 1990;8:113-8.
6. Bradford WZ, Christensen WN, Fraser H, et al. Treatment of Pure Tubular Carcinoma of the Breast. Breast J 1998;4:437-40.
7. Peters GN, Wolff M, Haagensen CD. Tubular carcinoma of the breast. Clinical pathologic correlations based on 100 cases. Ann Surg 1981;193:138-49.
8. Winchester DJ, Sahin AA, Tucker SL, et al. Tubular carcinoma of the breast. Predicting axillary nodal metastases and recurrence. Ann Surg 1996;223:342-7.
9. Cabral AH, Recine M, Paramo JC, et al. Tubular carcinoma of the breast: an institutional experience and review of the literature. Breast J 2003;9:298-301.
10. Sullivan T, Raad RA, Goldberg S, et al. Tubular carcinoma of the breast: a retrospective analysis and review of the literature. Breast Cancer Res Treat 2005;93:199-205.
11. Li B, Chen M, Nori D, et al. Adjuvant radiation therapy and survival for pure tubular breast carcinoma--experience from the SEER database. Int J Radiat Oncol Biol Phys 2012;84:23-9.
12. Poirier E, Desbiens C, Poirier B, et al. Characteristics and long-term survival of patients diagnosed with pure tubular carcinoma of the breast. J Surg Oncol 2018;117:1137-43.
13. Rakha EA, Lee AH, Evans AJ, et al. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. J Clin Oncol 2010;28:99-104.
14. Kitchen PR, Smith TH, Henderson MA, et al. Tubular carcinoma of the breast: prognosis and response to adjuvant systemic therapy. ANZ J Surg 2001;71:27-31.
15. Cong Y, Qiao G, Zou H, et al. Invasive cribriform carcinoma of the breast: A report of nine cases and a review of the literature. Oncol Lett 2015;9:1753-8.
16. Zhang W, Lin Z, Zhang T, et al. A pure invasive cribriform carcinoma of the breast with bone metastasis if untreated for thirteen years: a case report and literature review. World J Surg Oncol 2012;10:251.
17. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst 2009;101:736-50.
18. Colleoni M, Bagnardi V, Rotmensz N, et al. Increasing steroid hormone receptors expression defines breast cancer subtypes non responsive to preoperative chemotherapy. Breast Cancer Res Treat 2009;116:359-69.
19. Coates AS, Colleoni M, Goldhirsch A. Is Adjuvant Chemotherapy Useful for Women With Luminal A Breast Cancer? J Clin Oncol 2012;30:1260-3.
20. Colleoni M, Russo L, Dellapasqua S. Adjuvant therapies for special types of breast cancer. Breast 2011;20 Suppl 3:S153-7.
21. Khanfir K, Kallel A, Villette S, et al. Management of adenoid cystic carcinoma of the breast: a Rare Cancer Network study. Int J Radiat Oncol Biol Phys 2012;82:2118-24.
22. Elsner B. Adenoid cystic carcinoma of the breast. Review

of the literature and clinico-pathologic study of seven patients. Pathol Eur 1970;5:357-64.
23. Cavanzo FJ, Taylor HB. Adenoid cystic carcinoma of the breast. An analysis of 21 cases. Cancer 1969;24:740-5.
24. Leeming R, Jenkins M, Mendelsohn G. Adenoid cystic carcinoma of the breast. Arch Surg 1992;127:233-5.
25. Sumpio BE, Jennings TA, Merino MJ, et al. Adenoid cystic carcinoma of the breast. Data from the Connecticut Tumor Registry and a review of the literature. Ann Surg 1987;205:295-301.
26. Kleer CG, Oberman HA. Adenoid cystic carcinoma of the breast: value of histologic grading and proliferative activity. Am J Surg Pathol 1998;22:569-75.
27. Arpino G, Clark GM, Mohsin S, et al. Adenoid cystic carcinoma of the breast: molecular markers, treatment, and clinical outcome. Cancer 2002;94:2119-27.
28. Coates JM, Martinez SR, Bold RJ, et al. Adjuvant radiation therapy is associated with improved survival for adenoid cystic carcinoma of the breast. J Surg Oncol 2010;102:342-7.
29. Defaud-Henon F, Tunon-de-Lara C, Fournier M, et al. Adenoid cystic carcinoma of the breast: clinical, histological and immunohistochemical characterization. Ann Pathol 2010;30:7-16.
30. Kulkarni N, Pezzi CM, Greif JM, et al. Rare breast cancer: 933 adenoid cystic carcinomas from the National Cancer Data Base. Ann Surg Oncol 2013;20:2236-41.
31. Chae YK, Chung SY, Davis AA, et al. Adenoid cystic carcinoma: current therapy and potential therapeutic advances based on genomic profiling. Oncotarget 2015;6:37117-34.
32. Laurie SA, Ho AL, Fury MG, et al. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol 2011;12:815-24.
33. Papaspyrou G, Hoch S, Rinaldo A, et al. Chemotherapy and targeted therapy in adenoid cystic carcinoma of the head and neck: a review. Head Neck 2011;33:905-11.
34. Miyai K, Schwartz MR, Divatia MK, et al. Adenoid cystic carcinoma of breast: Recent advances. World J Clin Cases 2014;2:732-41.
35. Vranic S, Bender R, Palazzo J, et al. A review of adenoid cystic carcinoma of the breast with emphasis on its molecular and genetic characteristics. Hum Pathol 2013;44:301-9.
36. Abbasi S, Hopkins L. Treatment Challenges of Primary Acinic Cell Carcinoma of the Breast. J Curr Surg 2019;9:11-2.
37. Limite G, Di Micco R, Esposito E, et al. Acinic cell carcinoma of the breast: review of the literature. Int J Surg 2014;12 Suppl 1:S35-9.
38. Coyne JD, Dervan PA. Primary acinic cell carcinoma of the breast. J Clin Pathol 2002;55:545-7.
39. Chang ED, Lee EJ, Lee AW, et al. Primary acinic cell carcinoma of the breast: a case report with an immunohistochemical and ultrastructural studies. J Breast Cancer 2011;14:160-4.
40. Kulkarni N. Fine needle aspiration cytology of apocrine mammary carcinoma: Report of five cases. Oncyocytology 2012;2:6-9.
41. Tsutsumi Y. Apocrine Carcinoma as Triple-negative Breast Cancer: Novel Definition of Apocrine-type Carcinoma as Estrogen/Progesterone Receptor-negative and Androgen Receptor-positive Invasive Ductal Carcinoma. Jpn J Clin Oncol 2012;42:375-86.
42. Vranic S, Tawfik O, Palazzo J, et al. EGFR and HER-2/neu expression in invasive apocrine carcinoma of the breast. Mod Pathol 2010;23:644-53.
43. O'Malley FP, Bane A. An update on apocrine lesions of the breast. Histopathology 2008;52:3-10.
44. Tanaka K, Imoto S, Wada N, et al. Invasive Apocrine Carcinoma of the Breast: Clinicopathologic Features of 57 Patients. Breast J 2008;14:164-8.
45. Tomoya Nagao TK, Takashi Hojo, Hitoshi Tsuda, Kenji Tamura, Yasuhiro Fujiwara. 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 J 2012;21:289-95.
46. Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol 2006;24:1037-44.
47. 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;111:541-7.
48. Tan PH, Tse GM, Bay BH. Mucinous breast lesions: diagnostic challenges. J Clin Pathol 2008;61:11-9.
49. Diab SG, Clark GM, Osborne CK, et al. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol 1999;17:1442-8.
50. Komenaka IK, El-Tamer MB, Troxel A, et al. Pure mucinous carcinoma of the breast. Am J Surg 2004;187:528-32.
51. Anan K, Mitsuyama S, Tamae K, et al. Pathological features of mucinous carcinoma of the breast are favourable for breast-conserving therapy. Eur J Surg Oncol

2001;27:459-63.
52. Tavassoli FA, Devilee P. Pathology and Genetics: Tumours of the Breast and Female Genital Organs. WHO Classification of Tumours series - volume IV. Lyon, France: IARC Press. Breast Cancer Res 2004;6:133.
53. Andre S, Cunha F, Bernardo M, et al. Mucinous carcinoma of the breast: a pathologic study of 82 cases. J Surg Oncol 1995;58:162-7.
54. Shukla N, Roberts SS, Baki MO, et al. Successful Targeted Therapy of Refractory Pediatric ETV6-NTRK3 Fusion-Positive Secretory Breast Carcinoma. JCO Precis Oncol 2017. doi: 10.1200/PO.17.00034.
55. Ranade A, Batra R, Sandhu G, et al. Clinicopathological evaluation of 100 cases of mucinous carcinoma of breast with emphasis on axillary staging and special reference to a micropapillary pattern. J Clin Pathol 2010;63:1043-7.
56. Nakagawa T, Sato K, Moriwaki M, et al. Successful endocrine therapy for locally advanced mucinous carcinoma of the breast. Breast J 2012;18:632-3.
57. Mathew J, Agrawal A, Asgeirsson KS, et al. Primary endocrine therapy in locally advanced breast cancers--the Nottingham experience. Breast Cancer Res Treat 2009;113:403-7.
58. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007;110:244-54.
59. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev 2003;(2):CD002747.
60. Bae SY, Choi MY, Cho DH, et al. Mucinous Carcinoma of the Breast in Comparison with Invasive Ductal Carcinoma: Clinicopathologic Characteristics and Prognosis. J Breast Cancer 2011;14:308-13.
61. Yamaguchi J, Akashi-Tanaka S, Fukutomi T, et al. A case of mucinous carcinoma of the breast that demonstrated a good pathological response to neoadjuvant chemotherapy despite a poor clinical response. Breast Cancer 2006;13:100-3.
62. Ridolfi RL, Rosen PP, Port A, et al. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. Cancer 1977;40:1365-85.
63. Dreyer G, Vandorpe T, Smeets A, et al. Triple negative breast cancer: clinical characteristics in the different histological subtypes. Breast 2013;22:761-6.
64. Wong SL, Chao C, Edwards MJ, et al. Frequency of sentinel lymph node metastases in patients with favorable breast cancer histologic subtypes. Am J Surg 2002;184:492-8; discussion 498.
65. Jacob JD, Hodge C, Franko J, et al. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base. J Surg Oncol 2016;113:721-5.
66. Vieni S, Cabibi D, Cipolla C, et al. Secretory breast carcinoma with metastatic sentinel lymph node. World J Surg Oncol 2006;4:88.
67. Pohlodek K, Meciarova I, Grossmann P, et al. Secretory carcinoma of the breast: A case report. Int J Surg Case Rep 2019;56:74-7.
68. Horowitz DP, Sharma CS, Connolly E, et al. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. Breast 2012;21:350-3.
69. Herz H, Cooke B, Goldstein D. Metastatic secretory breast cancer. Non-responsiveness to chemotherapy: case report and review of the literature. Ann Oncol 2000;11:1343-7.
70. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106.
71. Collado-Mesa F, Net JM, Klevos GA, et al. Primary neuroendocrine carcinoma of the breast: report of 2 cases and literature review. Radiol Case Rep 2017;12:1-12.
72. Wang J, Wei B, Albarracin CT, et al. Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 2014;14:147.
73. Upalakalin JN, Collins LC, Tawa N, et al. Carcinoid tumors in the breast. Am J Surg 2006;191:799-805.
74. Lopez-Bonet E, Alonso-Ruano M, Barraza G, et al. Solid neuroendocrine breast carcinomas: incidence, clinico-pathological features and immunohistochemical profiling. Oncol Rep 2008;20:1369-74.
75. Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. Breast Care (Basel) 2013;8:149-54.
76. Makretsov N, Gilks CB, Coldman AJ, et al. Tissue microarray analysis of neuroendocrine differentiation and its prognostic significance in breast cancer. Hum Pathol 2003;34:1001-8.
77. Adams RW, Dyson P, Barthelmes L. Neuroendocrine breast tumours: breast cancer or neuroendocrine cancer presenting in the breast? Breast 2014;23:120-7.
78. Wade PM Jr, Mills SE, Read M, et al. Small cell neuroendocrine (oat cell) carcinoma of the breast. Cancer 1983;52:121-5.

79. Richter-Ehrenstein C, Arndt J, Buckendahl AC, et al. Solid neuroendocrine carcinomas of the breast: metastases or primary tumors? Breast Cancer Res Treat 2010;124:413-7.
80. Hare F, Giri S, Patel JK, et al. A population-based analysis of outcomes for small cell carcinoma of the breast by tumor stage and the use of radiation therapy. Springerplus 2015;4:138.
81. Wei B, Ding T, Xing Y, et al. Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. Cancer 2010;116:4463-73.
82. Wei X, Chen C, Xi D, et al. A case of primary neuroendocrine breast carcinoma that responded to neo-adjuvant chemotherapy. Front Med 2015;9:112-6.
83. Kinoshita S, Hirano A, Komine K, et al. Primary small-cell neuroendocrine carcinoma of the breast: report of a case. Surg Today 2008;38:734-8.
84. Nawawi O, Ying Goh K, Rahmat K. A rare case of primary infiltrating neuroendocrine carcinoma of the breast. Iran J Radiol 2012;9:212-6.
85. Oberg K. Management of neuroendocrine tumours. Ann Oncol 2004;15 Suppl 4:iv293-8.
86. Inno A, Bogina G, Turazza M, et al. Neuroendocrine Carcinoma of the Breast: Current Evidence and Future Perspectives. Oncologist 2016;21:28-32.
87. Roininen N, Takala S, Haapasaari KM, et al. Primary neuroendocrine breast carcinomas are associated with poor local control despite favourable biological profile: a retrospective clinical study. BMC Cancer 2017;17:72.
88. Alkaied H, Harris K, Azab B, et al. Primary neuroendocrine breast cancer, how much do we know so far? Med Oncol 2012;29:2613-8.
89. Takala S, Heikkila P, Nevanlinna H, et al. Metaplastic carcinoma of the breast: Prognosis and response to systemic treatment in metastatic disease. Breast J 2019;25:418-24.
90. Hu Q, Chen WX, Zhong SL, et al. Current progress in the treatment of metaplastic breast carcinoma. Asian Pac J Cancer Prev 2013;14:6221-5.
91. Dave G, Cosmatos H, Do T, et al. Metaplastic carcinoma of the breast: a retrospective review. Int J Radiat Oncol Biol Phys 2006;64:771-5.
92. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol 2011;18:94-103.
93. Pezzi CM, Patel-Parekh L, Cole K, et al. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol 2007;14:166-73.
94. Rayson D, Adjei AA, Suman VJ, et al. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol 1999;10:413-9.
95. Gutman H, Pollock RE, Janjan NA, et al. Biologic distinctions and therapeutic implications of sarcomatoid metaplasia of epithelial carcinoma of the breast. J Am Coll Surg 1995;180:193-9.
96. Zhang Y, Lv F, Yang Y, et al. Clinicopathological Features and Prognosis of Metaplastic Breast Carcinoma: Experience of a Major Chinese Cancer Center. PLoS One 2015;10:e0131409.
97. Tzanninis IG, Kotteas EA, Ntanasis-Stathopoulos I, et al. Management and Outcomes in Metaplastic Breast Cancer. Clin Breast Cancer 2016;16:437-43.
98. Chen IC, Lin CH, Huang CS, 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;130:345-51.
99. Rakha EA, Tan PH, Varga Z, et al. Prognostic factors in metaplastic carcinoma of the breast: a multi-institutional study. Br J Cancer 2015;112:283-9.
100. Bae SY, Lee SK, Koo MY, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Cancer Res Treat 2011;126:471-8.
101. Rauf F, Kiyani N, Bhurgri Y. Metaplastic carcinoma of the breast, an intriguing rarity. Asian Pac J Cancer Prev 2006;7:667-71.
102. Pal SK, Lau SK, Kruper L, et al. Papillary carcinoma of the breast: an overview. Breast Cancer Res Treat 2010;122:637-45.
103. Rakha EA, Ellis IO. Diagnostic challenges in papillary lesions of the breast. Pathology 2018;50:100-10.
104. Tan PH, Schnitt SJ, van de Vijver MJ, et al. Papillary and neuroendocrine breast lesions: the WHO stance. Histopathology 2015;66:761-70.
105. Liu ZY, Liu N, Wang YH, et al. Clinicopathologic characteristics and molecular subtypes of invasive papillary carcinoma of the breast: a large case study. J Cancer Res Clin Oncol 2013;139:77-84.
106. Rakha EA, Ahmed MA, Ellis IO. Papillary carcinoma of the breast: diagnostic agreement and management implications. Histopathology 2016;69:862-70.
107. Louwman MW, Vriezen M, van Beek MW, et al. Uncommon breast tumors in perspective: incidence, treatment and survival in the Netherlands. Int J Cancer 2007;121:127-35.
108. 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.
109. Vural O, Alnak A, Altundag K. Invasive papillary

carcinoma of the breast: an overview of twenty-four cases. Am Surg 2012;78:E144-5.
110. Solorzano CC, Middleton LP, Hunt KK, et al. Treatment and outcome of patients with intracystic papillary carcinoma of the breast. Am J Surg 2002;184:364-8.
111. Fayanju OM, Ritter J, Gillanders WE, et al. Therapeutic management of intracystic papillary carcinoma of the breast: the roles of radiation and endocrine therapy. Am J Surg 2007;194:497-500.
112. Mogal H, Brown DR, Isom S, et al. Intracystic papillary carcinoma of the breast: A SEER database analysis of implications for therapy. Breast 2016;27:87-92.
113. Calderaro J, Espie M, Duclos J, et al. Breast intracystic papillary carcinoma: an update. Breast J 2009;15:639-44.
114. Guo S, Wang Y, Rohr J, et al. Solid papillary carcinoma of the breast: A special entity needs to be distinguished from conventional invasive carcinoma avoiding over-treatment. Breast 2016;26:67-72.
115. Rakha EA, Gandhi N, Climent F, et al. Encapsulated papillary carcinoma of the breast: an invasive tumor with excellent prognosis. Am J Surg Pathol 2011;35:1093-103.
116. Gupta A, Sharma N, Jha AK, et al. Pleomorphic variant of lobular carcinoma breast: a rare case report with review of the literature. J Cancer Res Ther 2012;8:320-2.
117. Nguyen CV, Falcon-Escobedo R, Hunt KK, et al. Pleomorphic ductal carcinoma of the breast: predictors of decreased overall survival. Am J Surg Pathol 2010;34:486-93.
118. Butler D, Rosa M. Pleomorphic lobular carcinoma of the breast: a morphologically and clinically distinct variant of lobular carcinoma. Arch Pathol Lab Med 2013;137:1688-92.
119. Buchanan CL, Flynn LW, Murray MP, et al. Is pleomorphic lobular carcinoma really a distinct clinical entity? J Surg Oncol 2008;98:314-7.
120. Vargas AC, Lakhani SR, Simpson PT. Pleomorphic lobular carcinoma of the breast: molecular pathology and clinical impact. Future Oncol 2009;5:233-43.
121. Mahtani RL, Vogel CL. Pleomorphic lobular carcinoma of the breast: four long-term responders to trastuzumab--coincidence or hint? J Clin Oncol 2008;26:5823-4.
122. Monhollen L, Morrison C, Ademuyiwa FO, et al. Pleomorphic lobular carcinoma: a distinctive clinical and molecular breast cancer type. Histopathology 2012;61:365-77.
123. Aparicio I, Martinez A, Hernandez G, et al. Squamous cell carcinoma of the breast. Eur J Obstet Gynecol Reprod Biol 2008;137:222-6.
124. Behranwala KA, Nasiri N, Abdullah N, et al. Squamous cell carcinoma of the breast: clinico-pathologic implications and outcome. Eur J Surg Oncol 2003;29:386-9.
125. Hennessy BT, Krishnamurthy S, Giordano S, et al. Squamous cell carcinoma of the breast. J Clin Oncol 2005;23:7827-35.
126. Stevenson JT, Graham DJ, Khiyami A, et al. Squamous cell carcinoma of the breast: a clinical approach. Ann Surg Oncol 1996;3:367-74.
127. Zhu L, Chen K. Clinicopathological features, treatment patterns, and prognosis of squamous cell carcinoma of the breast: an NCDB analysis. BMC Cancer 2019;19:26.
128. Zhang X, Zhang B, Zang F, et al. Clinical features and treatment of squamous cell carcinoma of the breast. Onco Targets Ther 2016;9:3181-5.
129. Liu J, Yu Y, Sun JY, et al. Clinicopathologic characteristics and prognosis of primary squamous cell carcinoma of the breast. Breast Cancer Res Treat 2015;149:133-40.
130. Wu SG, Sun JY, Liu WM, et al. Effect of postoperative radiotherapy for squamous cell cancer of the breast in a surveillance epidemiology and end results population-based study. Oncotarget 2016;7:10684-93.
131. Dejager D, Redlich PN, Dayer AM, et al. Primary squamous cell carcinoma of the breast: sensitivity to cisplatinum-based chemotherapy. J Surg Oncol 1995;59:199-203.
132. Reis-Filho JS, Milanezi F, Carvalho S, 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:R1028-35.
133. Wang J, Zhang X, He J, et al. Co-expression of EGFR and CK5/6 in primary squamous cell carcinoma of the breast. Med Oncol 2014;31:172.
134. Sano D, Matsumoto F, Valdecanas DR, et al. Vandetanib restores head and neck squamous cell carcinoma cells' sensitivity to cisplatin and radiation in vivo and in vitro. Clin Cancer Res 2011;17:1815-27.
135. Zhao L, He LR, Xi M, et al. Nimotuzumab promotes radiosensitivity of EGFR-overexpression esophageal squamous cell carcinoma cells by upregulating IGFBP-3. J Transl Med 2012;10:249.

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