

Apocrine carcinoma of the breast: Review

Review

Chieh Yang¹, Irene Wang², Yun Yen^{3,4*}

¹University of California, Riverside, School of Medicine, Internal Medicine, USA

²University of California Riverside, School of Medicine, Family Medicine, USA

³Taipei Medical University, Taiwan

⁴Sino-American Cancer Foundation, USA

Received 7 June 2023; Accepted 31 July 2023

Abstract: Apocrine carcinoma of the breast is a rare subtype of breast carcinoma, which only presents as 4% among patients with breast cancer. The percentage varies based on the diagnostic criteria used by each institution to classify apocrine carcinoma. Several confusing terms used in previous studies, including apocrine ductal carcinoma in situ (ADCIS), apocrine morphology in lobular carcinoma in situ (Apocrine LCIS), apocrine-like invasive carcinoma, pure apocrine carcinoma, molecular apocrine tumors (MATs), and triple-negative apocrine carcinoma of the breast (TNAC). The treatment, prognosis, and molecular profiles are also diverse. Pure apocrine carcinoma has stricter criteria for diagnosis, requiring more than 90% of cells showing apocrine morphology and classic IHC characteristics of ER-negative, PR-negative, and AR-positive in at least 10% of tumor cell nuclei. Research related to prognosis is diverse due to the difficulty of unifying the diagnostic criteria. Current evidence of treatment is geared toward the use of neoadjuvant chemotherapy and anti-androgen therapy when AR is present, accompanied by other treatments if biomarkers are present, such as HER2, PI3K, or CDK4/6. This article focuses on clearly summarizing different subtypes and management of apocrine carcinoma of the breast.

Keywords: Apocrine carcinoma • breast cancer • androgen receptor

1. Introduction

Even though apocrine metaplasia is a common pathologic change seen in breast epithelial cells, apocrine breast carcinoma is a rare subtype of breast carcinoma, with a prevalence between 0.3% to 4%^[1-3]. As described in Figure 1, apocrine metaplasia could be separated into benign and malignant lesions. The premalignancy potential of benign metaplasia is still undetermined but may exist^[4,5]. Apocrine carcinoma is defined by >90% of tumor cells with apocrine morphology^[4]. The unique immunohistochemical profile shows progesterone receptor (PR) negative, estrogen receptor (ER) negative, and androgen receptor (AR) positive. Some apocrine carcinomas express HER2/neu or EGFR, which makes those patients eligible for targeted therapy, and some tumor cells express triple negativity, which usually presents moderate to high mitotic activity and behave more aggressively^[4,6,7].

In the study of Dellapasqua et al., the diagnosis of pure apocrine carcinoma was independently correlated

with a worsening disease-free survival^[8]. Apocrine carcinomas, both pure apocrine carcinoma and apocrine-like carcinoma, have an increased risk of contralateral breast cancer^[8]. In previous studies, apocrine carcinomas were more commonly found among the older population and without microcalcifications on mammography^[8-10]. Clinically, apocrine carcinomas more commonly present as palpable tumor masses and less commonly present as nipple discharge/bleeding^[4,11]. However, the rarity of apocrine breast cancer makes several topics related to apocrine carcinoma inconclusive, including the treatment and prognosis. In this article, we would like to summarize the current findings related to apocrine carcinoma of the breast.

2. Atypical apocrine lesions (AA)

Apocrine morphology is characterized as benign, atypical, or malignant^[12]. Atypical apocrine lesions (AA) are defined as a proliferation of apocrine cells

* E-mail: y Yen@tmu.edu.tw; yunyen@sacfaamerica.org

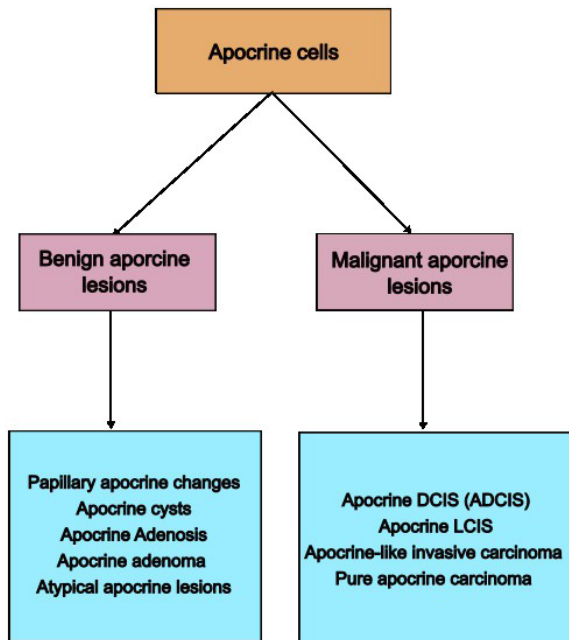


Figure 1: Classification of apocrine lesions in the breast.

with atypical cytomorphology but are difficult to be distinguished from non-high-grade apocrine ductal carcinoma in situ (ADCIS) since the lack of unified diagnosis criteria. However, generally, if the lesion had presented with necrosis, abnormal mitotic activity, and periductal changes, the diagnosis of ADCIS was more consistent^[12,13]. Due to the rarity of AA, follow-up studies, including those evaluating for transformation potential, of AA are also rare. In a study with 51 patients diagnosed as having atypical apocrine metaplasia in sclerosing lesions (AASL), none of the patients developed breast carcinoma during the follow-up period despite AASL typically being detectable by mammography^[14]. Another cohort of AASL also presented a low rate of subsequent carcinoma which was only 5.4% with a mean interval of 11.3 years^[15]. As mentioned above, those studies suggest that AASLs may not relate to an increased risk of following carcinoma, and further intervention may not require^[14-16].

3. Apocrine ductal carcinoma in situ (ADCIS) and Apocrine morphology in lobular carcinoma in situ (Apocrine LCIS)

Apocrine ductal carcinoma in situ (ADCIS) is a form of DCIS with apocrine morphology. This hormonal immunophenotype is usually androgen receptor-

positive, estrogen receptor-negative, and progesterone receptor-negative. In Leal's study, more than 90% of cases showed the above immunophenotype profile, and also they classified this category as ADCISs according to their nuclear grades and necrosis^[17]. ADCISs can be separated into high-grade ADCIS and non-high-grade ADCIS, but the latter is usually more challenging to recognize. Clinically, grades of ADCIS correlated with Ki67 proliferative index, human epidermal growth factor receptor-2 (HER2) expression, and the presence of accompanying invasive carcinoma^[12,17]. Apocrine morphology in lobular carcinoma in situ (LCIS) was defined as a solid intraductal proliferation of dyscohesive cells with intracytoplasmic vacuoles and abundant eosinophilic cytoplasm^[18]. In the study by Chen et al., cases presented most commonly among postmenopausal women were ER-negative, PR-negative, and Gross cystic disease fluid protein-15 (GCDFP)-positive^[18]. The summary of the immunophenotype profile of ADCIS is listed in Table 1.

4. Pure apocrine carcinoma

Apocrine carcinoma is rare, and the un-unifying diagnostic criteria in previous studies make the conclusion of prognosis and treatment choices become difficult. The diagnostic criteria of apocrine carcinoma involve two classifications: pure apocrine carcinoma and apocrine-like invasive carcinoma. Pure apocrine carcinoma is defined according to a strict criteria, including more than 90% of cells showing apocrine morphology and classic IHC characteristics of ER-negative, PR-negative, and AR-positive in at least 10% of tumor cell nuclei^[7]. In contrast, if a tumor only presents either morphology criteria **or** IHC criteria, it will be classified as apocrine-like invasive carcinoma. HER-2 could be either positive or negative in pure apocrine carcinoma, but the rate of HER-2 expression varied from one-third to more than half across different studies^[7,19]. HER2-positive pure apocrine carcinoma and HER2-negative pure apocrine carcinoma overlap with molecular apocrine tumors (MATs) and luminal androgen receptor tumors (LAR tumors), respectively^[7, 20-21] but not all LAR tumors and MATs showed apocrine morphology matching the diagnosis of pure apocrine carcinoma as in Figure 2. Molecular apocrine tumors were first described in 2005, with ER-negative, PR-negative, and high rates of AR signaling at the transcriptional level^[20]. Compared to the diagnosis criteria of apocrine carcinoma of ER-negative, ER- α 36 is the mRNA of an isoform of ER- α and is detectable in apocrine carcinoma of the breast. However, its use is limited, given the

Table 1: Immunohistochemistry characteristics of ADCIS and pure apocrine carcinoma.

IMMUNOHISTOLOGY MARKERS	PURE APOCRINE CARCINOMA	ADCIS	INVOLVING PATHWAY
ER, PR (-), AR (+)	100% strictly match to AR (+), ER(-), PR (-) criteria	>90%	AR pathway
HER-2	1/3 positive, 2/3 negative	47.1%	HER2 signaling pathway
GCDFP-15	75%	96.4%	AR pathway
AMACR	> 90%	> 90%	Oxidative degradation pathways
ER-A36	94.7%	94.7% (classified with pure apocrine carcinoma)	MAPK/ERK signaling pathway EGFR/Src/ERK signaling pathway
PIK3CA	>80%	100%	PI3K/mTOR pathway
P53	46-50%	61.8%	PI3K/mTOR/p53 pathway
PD-L1	10-40%	N/A	PD-1/PD-L1 pathway
AR-V7	57%	N/A	AR pathway

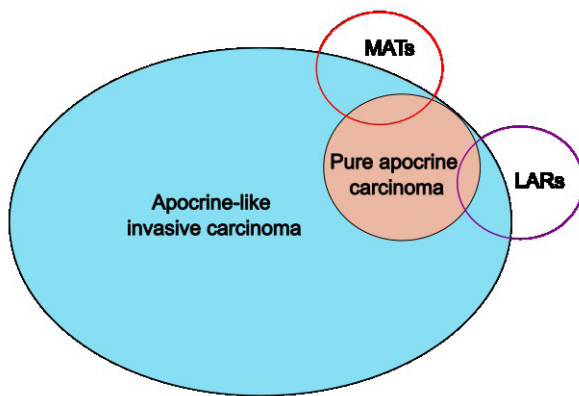


Figure 2: Illustration shows the relationship between apocrine carcinoma definitions.

inability to be identified by commercial antibodies due to the lack of antibody specificity^[22-23]. ER-α36 is one of the alternatively spliced isoforms of ER-α and is related to the activation of the mitogen-activated protein kinase (MAPK/ERK) signaling pathway, which showed stronger and more prolonged activation from anti-estrogens^[24]. EGFR/Src/ERK signaling pathway is also involved in the ER-α36 signaling^[25].

Except for the strict criteria to diagnose pure apocrine carcinoma, we would like to discuss other immunohistochemistry profiles of apocrine carcinoma. There are many immunohistochemistry markers that are related to the interaction of signaling pathways or can help with differential diagnosis. For example, HER2 amplification was identified in some cases with MATs, which may indicate a link between MATs and HER2 signaling^[7,20-21]. Despite the similarities, not all MATs fell fit within the criteria under pure apocrine carcinoma. For example, in a review of 58 patients with MATs, only 7% of cases had apocrine morphology^[26]. HER2's strong expression is

typically restricted to the malignant apocrine epithelium, but weak expression can be seen in atypical apocrine lesions^[27]. HER2 expression allowed for the possibility of target therapy but, unfortunately, also usually indicated a worse prognosis compared to TNBC^[28-29]. In some studies exploring expression, HER2 and GCDFP-15 were thought to be correlated with apocrine morphology and could increase the diagnostic sensitivity of MATs to 100%^[30-31]. GCDFP-15 is a product of the AR target gene regulated by the androgen receptor, which was reported positive in more than 75% of apocrine carcinoma in some studies^[32-33], and positive in 57% of MATs^[26]. The HER2/ERBB3 pathway was found to be involved in the regulation of androgen-related genes^[34]. Despite the lack of an established mechanism of crosstalk between HER2 and GCDFP-15, both are related to the AR pathway and AR-related gene expression^[32-35]. Another marker, α-Methylacyl-CoA racemase (AMACR, also known as P504S), was overexpressed in most breast carcinoma with apocrine differentiation^[36]. AMACR was >90% positive in both ADCIS or carcinomas with apocrine differentiation but seen significantly less in <22% of patients with non-apocrine carcinomas. Despite AMACR being similarly sensitive to GCDFP-15, AMACR had a higher specificity^[36]. There are also some other gene alterations potentially involved found in the study of Sun et al., such as PIK3CA, PTEN, and TP53. At least 88.9% of cases of triple-negative apocrine carcinoma (TNAC) present gene mutations involving the PI3K/mTOR pathway, and 72.2% of the patients with TNACs harboring PIK3CA mutations led to the theory that the PI3K inhibitor, Alpelisib, can also be targeted in treatment for TNAC^[37]. However, some evidence pointed out PIK3CA mutations' role in reducing sensitivity to trastuzumab, an anti-HER2 antibody, at the pathway level^[38]. This phenomenal

finding encouraged the further need for personalized genetic analysis of apocrine carcinoma. A significant negative correlation between Ki-67 and AR status has also been found^[31,39]. The percentage of p53 alternatives ranges between 46-50%, which possibly presents the degree of aggressiveness^[40-41]. The percentage of PD-L1 positivity is between 10-40%, but 78% of apocrine subtype TNBCs presented with MHC class I loss, which caused the possibility of less responsiveness to immunotherapy among this population since the checkpoint inhibitors' effectiveness relying on the presence of MHC class I^[37, 42-43]. Immunohistology characteristics of apocrine carcinoma are summarized in Table 1. The unique presentation of immunohistology markers in pure apocrine carcinoma of the breast can help with future diagnosis and be the possible target for treatment development.

4.1. Prognosis of apocrine carcinoma

Apocrine carcinoma prognosis has been debated and is difficult to ascertain since the current research uses different diagnostic criteria and the possibility that the prognosis depends on the risk factors and immunohistology markers. In a cohort study of Arciero, which included 566 patients with triple-negative apocrine carcinoma, showed a significantly improved long-term survival compared to the patients with triple-negative invasive ductal cancers^[44]. Regarding patients' characteristics, patients with TNAC are more likely to be Caucasian, older, and often presented with smaller, moderate to well-differentiated tumors^[44-46]. Some other studies, including patients with TNAC, also demonstrated a better 5-year OS and a significantly lower breast cancer-related death rate than patients with TNBC^[46-48]. Some research concluded a worse prognosis in populations with pure apocrine carcinoma than those with invasive ductal carcinoma, but some indicated a similar prognosis. In 2005, a study showed invasive apocrine carcinoma (IAC) of the breast has a similar prognosis compared to infiltrating ductal carcinoma, but the study didn't include immunohistology as a diagnostic criteria, making clinical applications challenging^[49]. In the study of Dellapasqua et al., the diagnosis of pure apocrine carcinoma correlated with worse disease-free survival compared with invasive ductal carcinoma (IDC), but apocrine-like breast cancer showed a similar outcome with IDC, which indicated the diversity of outcome of apocrine tumors might be related to the diagnosis criteria^[8]. In 2017, a single center cohort showed the overall survival and disease-free survival was similar between apocrine-like

carcinoma and pure apocrine carcinoma^[50]. Among the group with a diagnosis of MAT subtypes, the prognosis of the MAT subtype is poor compared to other subtypes and showed a 40% relapse rate within 5 years^[61]. In the study of Xu et al., they used a nomogram to predict OS in TNAC patients with five risk indicators, including age, stage, surgery, chemotherapy, and first malignant primary tumors, and presented a significantly different overall survival between the high-risk group and low-risk group^[46]. This result suggests that patients with TNAC, depending on risk factors, may be able to be separated into two groups, a high-risk group and a low-risk group, which can guide different treatment regimens.

4.2. AR expression and prognosis of apocrine carcinoma

There are variations in the AR-positive rate in triple-negative breast cancer (TNBC), and subsequently, the outcomes are diverse. In a cohort of TNBCs studied, AR expression was found in 17.7% of cases, with positive expression of AR correlated with older age, worse overall survival, and disease-free survival^[51]. In another retrospective study of TNBC, AR expression was found in 25.8% of cases, but AR expression was found to be a favorable prognostic factor of DFS and OS in patients with TNBC in this study^[52]. In the study of Ni et al., AR expression is enriched in ER-/HER2+ breast cancers, and they found AR would mediate the activation of HER2 signaling pathways, which suggested a potential therapeutic approach through a functional cross-talk between AR and ErbB2 pathway^[53-54]. The detail of cross-talk between the AR pathway and the ErbB2 pathway is demonstrated in Figure 3^[54]. In the study by Naderi, the cross-talk between FOXA1 and ErbB2 signaling pathways is also found among MACs^[55]. CAG repeats are found to be related to androgen receptor expression. The patients with more CAG repeats of the AR gene tend to have poor prognoses^[56], and two patients with ADCISs have very long CAG repeat lengths^[57]. This finding might contribute to the prediction of prognosis, but the AR+ population has not been totally included in the diagnosis of apocrine carcinoma since not all tumors with AR+ have apocrine morphology, and the demonstration of classification is in Figure 2.

5. Apocrine-like invasive carcinoma

The classification of this group, apocrine-like carcinoma, is created for tumors that can't be classified to either one of the above diagnoses, such as atypical

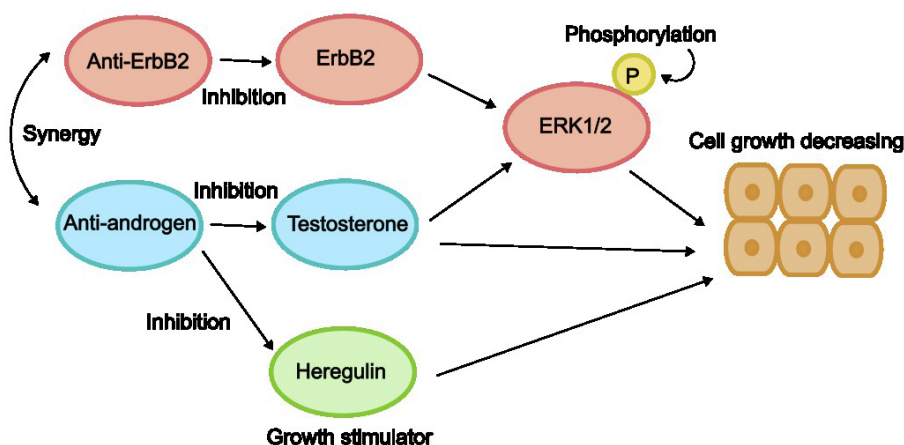


Figure 3: The Cross-talk of AR and ErbB2 pathways In Naderi's study, the function of ERK1/2, testosterone, and Heregulin can be suppressed by both AR and ErbB2 pathways. Anti-ErbB2 and anti-androgen therapy can inhibit the function of testosterone and ErbB2 and further cause the phosphorylation of ERK1/2, followed by negative regulation of cell growth. [52]

apocrine lesions, apocrine ductal carcinoma in situ (ADCIS), apocrine morphology in lobular carcinoma in situ (Apocrine LCIS) or pure apocrine carcinoma. As mentioned above, this category usually includes invasive carcinomas that fit into either morphology criteria or IHC criteria, but not both and thus are not able to be classified as pure apocrine carcinomas^[7]. As described in Figure 2, part of MATs and LARs can be classified in this group but usually are classified as MATs or LARs in different research. As a result, pure evidence of treatment and prognosis of apocrine-like carcinoma are rare and challenging due to the variable diagnosis criteria studies used. The prognosis varies based on the criteria used and will present either a worse or similar outcome compared to ductal carcinoma^[8,50].

6. Treatment

6.1. Atypical apocrine lesions (AAs) and ADCISs

Since atypical apocrine lesions only carry a low rate of transformation to carcinoma or hold no increased risk, further interventions may not be required^[14-16]. However, given the diagnostic difficulty between AAs and ADCISs, a core needle biopsy might be required^[12]. ADCISs are separated into high-grade ADCISs and non-high-grade ADCISs, and high-grade ADCISs are more aggressive. In the study by Leal et al., most patients with ADCISs received mastectomy or conservative surgery followed by adjuvant radiation therapy if they didn't receive a complete mastectomy, and no recurrence was found during the median follow-up of 37 months^[17]. Though high-grade ADCISs may need more aggressive

management, current evidence has been insufficient. Currently, no evidence supports the use of anti-androgen therapy among the population with ADCISs. The summary of the intervention is in Table 2.

6.2. Apocrine carcinoma

Neoadjuvant therapy is commonly applied to patients with invasive apocrine carcinoma of the breast, and the measured pathologic complete response rate varied from 14.3% to 33%, depending on the classification definition of invasive apocrine carcinoma^[50, 58-59]. A study also found patients with triple-negative breast cancers and AR+ had a lower pathologic complete response rate after neoadjuvant chemotherapy than those with AR^[60]. In contrast, in EORTC 10994/BIG 1-00, a phase III study, the highest pCR rates were found among groups of MA and triple-negative basal-like carcinoma, 33.3% and 34%, respectively, and indicated that the diversity of pCR rates in different studies is attributed to different classification and definition of diagnosis^[61]. Due to the older median age of diagnosis of patients with TNAC, fewer patients received chemotherapy overall, and in one study, as low as 59.79% of patients received chemotherapy^[46]. There is some evidence showing that chemotherapy can improve the prognosis of patients with TNAC^[62]. In the study by Vranic et al., the authors also mentioned that due to the variable expression of biomarkers of traditional chemotherapy in patients with apocrine carcinoma, personalized analysis of biomarkers may best optimize chemotherapy^[63].

The effectiveness of anti-androgen therapy is controversial in the population with apocrine carcinoma with AR+ since most studies include not only apocrine

Table 2: Treatment recommendation from the literature review.

CLASSIFICATION	INTERVENTION
ATYPICAL APOCRINE LESIONS (AA)	No intervention +/- Core needle biopsy
APOCRINE DCIS (ADCIS)	Mastectomy or conservative surgery +/- adjuvant radiation therapy
APOCRINE CARCINOMA	Neoadjuvant chemotherapy + surgery +/- radiation therapy + anti-androgen therapy (if AR+) + anti-HER2 antibodies (if HER2+) +/- PI3 kinase inhibition and CDK4/6 inhibitors (if biomarkers detected)

carcinoma but also other AR+ breast cancers. A phase II clinical trial showed a 19% clinical benefit rate among patients with AR+/PR-/ER- treated with bicalutamide, an anti-androgen therapy^[64]. In the phase II trial mentioned above, the use of the AR antagonist, bicalutamide, in patients with AR+, ER/PgR-negative advanced breast cancer showed a 19% of clinical benefit rate, but this study didn't focus on the apocrine carcinoma of the breast^[64]. On the other hand, a clinical trial in 2020 demonstrated that bicalutamide in combination with another aromatase inhibitor (AI) used in patients with ER-positive breast cancer with AI resistance did not show synergistic activity^[65]. Similar to the above studies, most studies target triple-negative breast cancer with AR-positive^[66-68], and more evidence is required to standardize anti-androgen therapy in apocrine carcinoma. TNBC with apocrine morphology showed a high frequency of mutation in PIK3CA and other PI3K signaling pathways, and the combined use of PI3K inhibitors plus AR antagonists resulted in a significant reduction of cell line models^[69-70]. In a phase Ib/II clinical trial, the combination of enzalutamide and Taselisib showed increasing clinical benefit in patients with TNBC and AR+, especially in the LAR subtype, with 75% clinical benefit, which is higher than other subtypes^[71]. LAR tumors are also susceptible to CDK4/6 inhibitors compared with basal-like tumors and PI3 kinase inhibition synergizing with CDK4/6 inhibitors^[72].

Due to the inclusion criteria difference among trials and studies, current pieces of evidence focus more on TNBC with AR+. Neoadjuvant chemotherapy presents evidence of improving outcomes followed by surgery in TNACs, and anti-androgen therapy can also be considered if tumors show AR+. Additionally, PI3 kinase and CDK4/6 inhibitors can be added as additional treatments if tumors show corresponding markers. However, further evidence focusing on pure apocrine carcinoma is needed to support standard management. Personalized biomarkers analysis and prognosis factors analysis is promising in predicting prognosis and therapy adjustment. The summary of the intervention for apocrine carcinoma is in Table 2.

6.3. Resistance

Androgen receptor splicing variant-7 (AR-V7) involves resistance mechanisms against anti-androgen treatment in prostate cancers but is found to be applicable to breast cancers^[73,74]. In the study by Ferguson, AR-V7 positive cases demonstrated a significantly higher percentage of apocrine morphology compared to AR-V7 negative cases, which are 42.1% versus 3.4%, respectively^[73]. AR-V7 can be presented in the nucleus to bypass the exposure of androgen and is not altered by anti-androgen therapy. AR-V7s have also been found present in primary breast cancer without previous exposure to anti-androgen therapy^[72-74]. The study also noted that molecular testing for AR-V7 may be considered in breast cancers with apocrine morphology or AR+ before starting the anti-androgen treatment^[73]. Due to these characteristics, AR-V7 may predict prognosis before starting anti-androgen therapy, but there is still a lack of evidence or clinical trials to support this hypothesis. Currently, evidence supports the focus on exploring anti-androgen therapy, but if additional clinical trials result support the predictive value of AR-V7, we can consider the detection of AR-V7 in the population of AR+ breast cancer to predict the effectiveness of anti-androgen to help clinical decisions.

7. Conclusion

Several immunohistologic characteristics found among apocrine carcinomas have been explored, affecting treatment options. The current body of treatment evidence has been more focused on the use of neoadjuvant chemotherapy and anti-androgen therapy when AR is present and accompanied by other treatments if biomarkers are present, such as HER2, PI3K, or CDK4/6. The prognosis of apocrine carcinoma is still diverse in different studies. Personalized biomarkers analysis and prognosis factors analysis is promising in the prediction of prognosis and therapy adjustment for apocrine carcinoma.

Conflict of Interest Statement

The authors whose names are listed in the title page certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript

References

- [1] Mossler JA, Barton TK, Brinkhous AD, McCarty KS, Moylan JA, McCarty KS Jr. Apocrine differentiation in human mammary carcinoma. *Cancer*. 1980;46(11):2463-2471. doi:10.1002/1097-0142(19801201)46:11<2463::aid-cnrcr2820461127>3.0.co;2-#
- [2] Eusebi V, Millis RR, Cattani MG, Bussolati G, Azzopardi JG. Apocrine carcinoma of the breast. A morphologic and immunocytochemical study [published correction appears in *Am J Pathol* 1986 Sep;124(3): following 563]. *Am J Pathol*. 1986;123(3):532-541.
- [3] Durham JR, Fechner RE. The Histologic Spectrum of Apocrine Lesions of the Breast. *Am J Clin Pathol*. 2000;113(suppl_1):S3-S18. doi:10.1309/7A2P-YMWJ-B1PD-UDN9
- [4] Vranic S, Schmitt F, Sapino A, et al. Apocrine carcinoma of the breast: a comprehensive review. *Histol Histopathol*. 2013;28(11):1393-1409. doi:10.14670/HH-28.1393
- [5] Selim AG, El-Ayat G, Wells CA. c-erbB2 oncoprotein expression, gene amplification, and chromosome 17 aneusomy in apocrine adenosis of the breast. *J Pathol*. 2000;191(2):138-142. doi:10.1002/(SICI)1096-9896(200006)191:2<138::AID-PATH611>3.0.CO;2-J
- [6] Choi J, Jung WH, Koo JS. Clinicopathologic features of molecular subtypes of triple negative breast cancer based on immunohistochemical markers. *Histol Histopathol*. 2012;27(11):1481-1493. doi:10.14670/HH-27.1481
- [7] 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(5):644-653. doi:10.1038/modpathol.2010.50
- [8] Dellapasqua S, Maisonneuve P, Viale G, et al. Immunohistochemically defined subtypes and outcome of apocrine breast cancer. *Clin Breast Cancer*. 2013;13(2):95-102. doi:10.1016/j.clbc.2012.11.004
- [9] Matsuo K, Fukutomi T, Tsuda H, Kanai Y, Tanaka SA, Nanasawa T. Apocrine Carcinoma of the Breast: Clinicopathological Analysis and Histological Subclassification of 12 Cases. *Breast Cancer*. 1998;5(3):279-284. doi:10.1007/BF02966708
- [10] Honma N, Sakamoto G, Akiyama F, et al. Breast carcinoma in women over the age of 85: distinct histological pattern and androgen, oestrogen, and progesterone receptor status. *Histopathology*. 2003;42(2):120-127. doi:10.1046/j.1365-2559.2003.01542.x
- [11] Gilles R, Lesnik A, Guinebretière JM, et al. Apocrine carcinoma: clinical and mammographic features. *Radiology*. 1994;190(2):495-497. doi:10.1148/radiology.190.2.8284405
- [12] D'Arcy C, Quinn C. Apocrine lesions of the breast: part 1 of a two-part review: benign, atypical and in situ apocrine proliferations of the breast. *J Clin Pathol*. 2019;72(1):1-6. doi:10.1136/jclinpath-2018-205484
- [13] Tavassoli FA, Norris HJ. Intraductal apocrine carcinoma: a clinicopathologic study of 37 cases. *Mod Pathol*. 1994;7(8):813-818.
- [14] Carter DJ, Rosen PP. Atypical apocrine metaplasia in sclerosing lesions of the breast: a study of 51 patients. *Mod Pathol*. 1991;4(1):1-5.
- [15] Fuehrer N, Hartmann L, Degnim A, et al. Atypical apocrine adenosis of the breast: long-term follow-up in 37 patients. *Arch Pathol Lab Med*. 2012;136(2):179-182. doi:10.5858/arpa.2011-0225-OA

- [16] Calhoun, B.C., & Booth, C.N. (2014). Atypical apocrine adenosis diagnosed on breast core biopsy: implications for management. *Human pathology*, 45 10, 2130-5 .
- [17] Leal C, Henrique R, Monteiro P, et al. Apocrine ductal carcinoma in situ of the breast: histologic classification and expression of biologic markers. *Hum Pathol*. 2001;32(5):487-493. doi:10.1053/hupa.2001.24327
- [18] Chen YY, Hwang ES, Roy R, et al. Genetic and phenotypic characteristics of pleomorphic lobular carcinoma in situ of the breast. *Am J Surg Pathol*. 2009;33(11):1683-1694. doi:10.1097/PAS.0b013e3181b18a89
- [19] Xu Y, Zhang W, He J, et al. Nomogram for predicting overall survival in patients with triple-negative apocrine breast cancer: Surveillance, epidemiology, and end results-based analysis. *Breast*. 2022;66:8-14. doi:10.1016/j.breast.2022.08.011
- [20] Farmer P, Bonnefoi H, Becette V, et al. Identification of molecular apocrine breast tumours by microarray analysis. *Oncogene*. 2005;24(29):4660-4671. doi:10.1038/sj.onc.1208561
- [21] D'Arcy C, Quinn CM. Apocrine lesions of the breast: part 2 of a two-part review. Invasive apocrine carcinoma, the molecular apocrine signature and utility of immunohistochemistry in the diagnosis of apocrine lesions of the breast. *J Clin Pathol*. 2019;72(1):7-11. doi:10.1136/jclinpath-2018-205485
- [22] Vranic S, Gatalica Z, Deng H, et al. ER- α 36, a novel isoform of ER- α 66, is commonly over-expressed in apocrine and adenoid cystic carcinomas of the breast. *J Clin Pathol*. 2011;64(1):54-57. doi:10.1136/jcp.2010.082776
- [23] Bratthauer GL, Lininger RA, Man YG, Tavassoli FA. Androgen and estrogen receptor mRNA status in apocrine carcinomas. *Diagn Mol Pathol*. 2002;11(2):113-118. doi:10.1097/00019606-200206000-00008
- [24] Wang Z, Zhang X, Shen P, Loggie BW, Chang Y, Deuel TF. A variant of estrogen receptor- $\{\alpha\}$, hER- $\{\alpha\}$ 36: transduction of estrogen- and antiestrogen-dependent membrane-initiated mitogenic signaling. *Proc Natl Acad Sci U S A*. 2006;103(24):9063-9068. doi:10.1073/pnas.0603339103
- [25] Zhang XT, Kang LG, Ding L, Vranic S, Gatalica Z, Wang ZY. A positive feedback loop of ER- α 36/EGFR promotes malignant growth of ER-negative breast cancer cells. *Oncogene*. 2011;30(7):770-780. doi:10.1038/onc.2010.458
- [26] Lehmann-Che J, Hamy AS, Porcher R, et al. Molecular apocrine breast cancers are aggressive estrogen receptor negative tumors overexpressing either HER2 or GCDFP15. *Breast Cancer Res*. 2013;15(3):R37. Published 2013 May 11. doi:10.1186/bcr3421
- [27] Wells CA, El-Ayat GA. Non-operative breast pathology: apocrine lesions. *J Clin Pathol*. 2007;60(12):1313-1320. doi:10.1136/jcp.2006.040626
- [28] Arciero CA, Diehl AH 3rd, Liu Y, et al. Triple-negative apocrine carcinoma: A rare pathologic subtype with a better prognosis than other triple-negative breast cancers. *J Surg Oncol*. 2020;122(6):1232-1239. doi:10.1002/jso.26129
- [29] Ismail S, Kherbek H, Skef J, Zahlouk N, Abdulal R, Alshehabi Z. Triple-negative apocrine carcinoma as a rare cause of a breast lump in a Syrian female: a case report and review of the literature. *BMC Womens Health*. 2021;21(1):396. Published 2021 Nov 25. doi:10.1186/s12905-021-01539-3
- [30] Darb-Esfahani S, von Minckwitz G, Denkert C, et al. Gross cystic disease fluid protein 15 (GCDFP-15) expression in breast cancer subtypes. *BMC Cancer*. 2014;14:546. Published 2014 Jul 28. doi:10.1186/1471-2407-14-546
- [31] Vranic S, Marchiò C, Castellano I, et al. Immunohistochemical and molecular profiling of histologically defined apocrine carcinomas of the breast. *Hum Pathol*. 2015;46(9):1350-1359. doi:10.1016/j.humpath.2015.05.017
- [32] Mazoujian G, Pinkus GS, Davis S, Haagensen DE Jr. Immunohistochemistry of a gross cystic disease fluid protein (GCDFP-15) of the breast. A marker of apocrine epithelium and breast carcinomas with apocrine features. *Am J Pathol*. 1983;110(2):105-112.
- [33] Honma N, Takubo K, Akiyama F, et al. Expression of GCDFP-15 and AR decreases in larger or node-positive apocrine carcinomas of the breast. *Histopathology*. 2005;47(2):195-201. doi:10.1111/j.1365-2559.2005.02181.x
- [34] Mellinghoff IK, Vivanco I, Kwon A, Tran C, Wongvipat J, Sawyers CL. HER2/neu kinase-dependent modulation of androgen receptor function through effects on DNA binding and stability. *Cancer Cell*. 2004;6(5):517-527. doi:10.1016/j.ccr.2004.09.031
- [35] Darb-Esfahani S, von Minckwitz G, Denkert C, et al. Gross cystic disease fluid protein 15 (GCDFP-15) expression in breast cancer subtypes. *BMC Cancer*. 2014;14:546. Published 2014 Jul 28. doi:10.1186/1471-2407-14-546

- [36] Nakamura H, Kukita Y, Kunimasa K, et al. α -Methylacyl-CoA racemase: a useful immunohistochemical marker of breast carcinoma with apocrine differentiation. *Hum Pathol.* 2021;116:39-48. doi:10.1016/j.humpath.2021.07.005
- [37] Sun X, Zuo K, Yao Q, et al. Invasive apocrine carcinoma of the breast: clinicopathologic features and comprehensive genomic profiling of 18 pure triple-negative apocrine carcinomas. *Mod Pathol.* 2020;33(12):2473-2482. doi:10.1038/s41379-020-0589-x
- [38] Shi W, Jiang T, Nuciforo P, et al. Pathway level alterations rather than mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial [published correction appears in *Ann Oncol.* 2018 Apr 1;29(4):1075] [published correction appears in *Ann Oncol.* 2018 Oct 1;29(10):2152] [published correction appears in *Ann Oncol.* 2019 Jan 9;]. *Ann Oncol.* 2017;28(1):128-135. doi:10.1093/annonc/mdw434
- [39] McNamara KM, Yoda T, Miki Y, et al. Androgenic pathway in triple negative invasive ductal tumors: its correlation with tumor cell proliferation. *Cancer Sci.* 2013;104(5):639-646. doi:10.1111/cas.12121
- [40] O'Malley FP, Bane A. An update on apocrine lesions of the breast. *Histopathology.* 2008;52(1):3-10. doi:10.1111/j.1365-2559.2007.02888.x
- [41] Yerushalmi R, Hayes MM, Gelmon KA. Breast carcinoma--rare types: review of the literature. *Ann Oncol.* 2009;20(11):1763-1770. doi:10.1093/annonc/mdp245
- [42] Dusenbery AC, Maniaci JL, Hillerson ND, Dill EA, Bullock TN, Mills AM. MHC Class I Loss in Triple-negative Breast Cancer: A Potential Barrier to PD-1/PD-L1 Checkpoint Inhibitors. *Am J Surg Pathol.* 2021;45(5):701-707. doi:10.1097/PAS.0000000000001653
- [43] Vranic S, Gatalica Z. An Update on the Molecular and Clinical Characteristics of Apocrine Carcinoma of the Breast. *Clin Breast Cancer.* 2022;22(4):e576-e585. doi:10.1016/j.clbc.2021.12.009
- [44] Arciero CA, Diehl AH 3rd, Liu Y, et al. Triple-negative apocrine carcinoma: A rare pathologic subtype with a better prognosis than other triple-negative breast cancers. *J Surg Oncol.* 2020;122(6):1232-1239. doi:10.1002/jso.26129
- [45] Mills AM, E Gottlieb C, M Wendroth S, M Brenin C, Atkins KA. Pure Apocrine Carcinomas Represent a Clinicopathologically Distinct Androgen Receptor-Positive Subset of Triple-Negative Breast Cancers. *Am J Surg Pathol.* 2016;40(8):1109-1116. doi:10.1097/PAS.0000000000000671
- [46] Xu Y, Zhang W, He J, et al. Nomogram for predicting overall survival in patients with triple-negative apocrine breast cancer: Surveillance, epidemiology, and end results-based analysis. *Breast.* 2022;66:8-14. doi:10.1016/j.breast.2022.08.011
- [47] Wu W, Wu M, Peng G, Shi D, Zhang J. Prognosis in triple-negative apocrine carcinomas of the breast: A population-based study. *Cancer Med.* 2019;8(18):7523-7531. doi:10.1002/cam4.2634
- [48] Meattini I, Pezzulla D, Saieva C, et al. Triple Negative Apocrine Carcinomas as a Distinct Subtype of Triple Negative Breast Cancer: A Case-control Study. *Clin Breast Cancer.* 2018;18(5):e773-e780. doi:10.1016/j.clbc.2018.02.012
- [49] Japaze H, Emina J, Diaz C, et al. 'Pure' invasive apocrine carcinoma of the breast: a new clinicopathological entity?. *Breast.* 2005;14(1):3-10. doi:10.1016/j.breast.2004.06.003
- [50] Imamovic D, Bilalovic N, Skenderi F, et al. A clinicopathologic study of invasive apocrine carcinoma of the breast: A single-center experience. *Breast J.* 2018;24(6):1105-1108. doi:10.1111/tbj.13140
- [51] Choi JE, Kang SH, Lee SJ, Bae YK. Androgen receptor expression predicts decreased survival in early stage triple-negative breast cancer. *Ann Surg Oncol.* 2015;22(1):82-89. doi:10.1245/s10434-014-3984-z
- [52] He J, Peng R, Yuan Z, et al. Prognostic value of androgen receptor expression in operable triple-negative breast cancer: a retrospective analysis based on a tissue microarray. *Med Oncol.* 2012;29(2):406-410. doi:10.1007/s12032-011-9832-0
- [53] Ni M, Chen Y, Lim E, et al. Targeting androgen receptor in estrogen receptor-negative breast cancer. *Cancer Cell.* 2011;20(1):119-131. doi:10.1016/j.ccr.2011.05.026
- [54] Naderi A, Hughes-Davies L. A functionally significant cross-talk between androgen receptor and ErbB2 pathways in estrogen receptor-negative breast cancer. *Neoplasia.* 2008;10(6):542-548. doi:10.1593/neo.08274
- [55] Naderi A, Meyer M, Dowhan DH. Cross-regulation between FOXA1 and ErbB2 signaling in estrogen receptor-negative breast cancer. *Neoplasia.* 2012;14(4):283-296. doi:10.1593/neo.12294
- [56] Lee YT, Liu HM, Lee LH, et al. The polymorphism of CAG repeats in the androgen receptor gene and breast cancer mortality. *Cancer Biomark.* 2015;15(6):815-822. doi:10.3233/CBM-150525
- [57] Kasami M, Gobbi H, Dupont WD, Simpson JF, Page DL, Vnencak-Jones CL. Androgen receptor CAG

- repeat lengths in ductal carcinoma in situ of breast, longest in apocrine variety. *Breast*. 2000;9(1):23-27. doi:10.1054/brst.1999.0070
- [58] Santonja A, Sánchez-Muñoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. *Oncotarget*. 2018;9(41):26406-26416. Published 2018 May 29. doi:10.18632/oncotarget.25413
- [59] Echavarria I, López-Tarruella S, Picornell A, et al. Pathological Response in a Triple-Negative Breast Cancer Cohort Treated with Neoadjuvant Carboplatin and Docetaxel According to Lehmann's Refined Classification. *Clin Cancer Res*. 2018;24(8):1845-1852. doi:10.1158/1078-0432.CCR-17-1912
- [60] Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: Correlation between Androgen Receptor Expression and Pathological Response. *Asian Pac J Cancer Prev*. 2020;21(2):563-568. Published 2020 Feb 1. doi:10.31557/APJCP.2020.21.2.563
- [61] Bonnefoi H, MacGrogan G, Poncet C, et al. Molecular apocrine tumours in EORTC 10994/BIG 1-00 phase III study: pathological response after neoadjuvant chemotherapy and clinical outcomes. *Br J Cancer*. 2019;120(9):913-921. doi:10.1038/s41416-019-0420-y
- [62] Altundag K. De-escalating systemic chemotherapy might be considered for pure triple negative apocrine breast cancer patients. *J BUON*. 2019;24(2):864.
- [63] Vranic S, Feldman R, Gatalica Z. Apocrine carcinoma of the breast: A brief update on the molecular features and targetable biomarkers. *Bosn J Basic Med Sci*. 2017;17(1):9-11. Published 2017 Feb 21. doi:10.17305/bjbm.2016.1811
- [64] Gucalp A, Tolaney S, Isakoff SJ, et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. *Clin Cancer Res*. 2013;19(19):5505-5512. doi:10.1158/1078-0432.CCR-12-3327
- [65] Lu Q, Xia W, Lee K, et al. Bicalutamide plus Aromatase Inhibitor in Patients with Estrogen Receptor-Positive/Androgen Receptor-Positive Advanced Breast Cancer. *Oncologist*. 2020;25(1):21-e15. doi:10.1634/theoncologist.2019-0564
- [66] Cipriano É, Mesquita A. Emerging Therapeutic Drugs in Metastatic Triple-Negative Breast Cancer. *Breast Cancer (Auckl)*. 2021;15:11782234211002491. Published 2021 Mar 22. doi:10.1177/11782234211002491
- [67] Bonnefoi H, Grellety T, Tredan O, et al. A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1). *Ann Oncol*. 2016;27(5):812-818. doi:10.1093/annonc/mdw067
- [68] Traina T. A., Miller K., Yardley D. A., Eakle J., Schwartzberg L. S. & O'Shaughnessy J. et al. Enzalutamide for the treatment of androgen receptor-expressing triple-negative breast cancer. *J. Clin. Oncol*. 36, 884–890 (2018).
- [69] Weisman PS, Ng CK, Brogi E, et al. Genetic alterations of triple negative breast cancer by targeted next-generation sequencing and correlation with tumor morphology. *Mod Pathol*. 2016;29(5):476-488. doi:10.1038/modpathol.2016.39
- [70] Lehmann BD, Bauer JA, Schafer JM, et al. PIK3CA mutations in androgen receptor-positive triple negative breast cancer confer sensitivity to the combination of PI3K and androgen receptor inhibitors. *Breast Cancer Res*. 2014;16(4):406. Published 2014 Aug 8. doi:10.1186/s13058-014-0406-x
- [71] Lehmann BD, Abramson VG, Sanders ME, et al. TBCRC 032 IB/II Multicenter Study: Molecular Insights to AR Antagonist and PI3K Inhibitor Efficacy in Patients with AR+ Metastatic Triple-Negative Breast Cancer. *Clin Cancer Res*. 2020;26(9):2111-2123. doi:10.1158/1078-0432.CCR-19-2170
- [72] Asghar US, Barr AR, Cutts R, et al. Single-Cell Dynamics Determines Response to CDK4/6 Inhibition in Triple-Negative Breast Cancer. *Clin Cancer Res*. 2017;23(18):5561-5572. doi:10.1158/1078-0432.CCR-17-0369
- [73] Ferguson DC, Mata DA, Tay TK, et al. Androgen receptor splice variant-7 in breast cancer: clinical and pathologic correlations. *Mod Pathol*. 2022;35(3):396-402. doi:10.1038/s41379-021-00924-5
- [74] Hickey TE, Irvine CM, Dvinge H, et al. Expression of androgen receptor splice variants in clinical breast cancers. *Oncotarget*. 2015;6(42):44728-44744. doi:10.18632/oncotarget.6296
- [75] Hickey TE, Robinson JL, Carroll JS, Tilley WD. Minireview: The androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene?. *Mol Endocrinol*. 2012;26(8):1252-1267. doi:10.1210/me.2012-1107
- [76] Schwartz CJ, Ruiz J, Bean GR, et al. Triple-Negative Apocrine Carcinomas: Toward a Unified Group With Shared Molecular Features and Clinical Behavior. *Mod Pathol*. 2023;36(5):100125. doi:10.1016/j.modpat.2023.100125