Original Study

Disease Behavior and Treatment Response of Special Histological Types of Triple-Negative Breast Cancer

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Abstract

Special histological types of triple-negative breast cancer encompass rare diseases with distinct behavior.
With 132 patients, our results reinforce the diversity of the clinical features and treatment response of these diseases.
The poor prognosis of metaplastic and lobular carcinomas contrasts with the favorable outcomes of medullary and apocrine carcinomas.
Treatment strategies focused on the particularities of each special type are required.

Background: : Special histological types (SHT) of triple-negative breast cancer (TNBC) are a heterogeneous group of rare poorly understood diseases. We aimed to evaluate the clinical features, treatment, and outcomes of patients with SHT of TNBC. **Methods:** : We evaluated patients with a SHT of TNBC treated in a cancer center between 2009 and 2020. The endpoints were characterization of clinical and pathological features, pathologic complete response (PCR) rate after neoadjuvant chemotherapy, disease-free survival (DFS), progression-free survival, and overall survival (OS). **Results:** : The 132 patients included had the following histologies: metaplastic (n=71), medullary pattern (n=14), lobular (n=12), adenoid cystic (n=12), apocrine (n=10), and others (n=13). Metaplastic, lobular, and medullary pattern tumors had higher grade (66.6–85.7% grade 3); adenoid cystic and apocrine had mainly grade 1-2 (70–83.3%). Metaplastic and lobular carcinomas had higher disease stages (47.8% and 58.2% stages III-IV). PCR rates were 10.3% for metaplastic and 33.3% for lobular carcinomas, with 5-year DFS rates of 56% and 51.4%. Medullary pattern carcinomas had a great response to treatment, with PCR rate of 100%, and 5-year DFS rate of 92.8%. Apocrine carcinomas also had favorable prognosis, with no recurrence after early disease treatment, and 5-year DFS rate of 83.3%. Adenoid cystic carcinomas had intermediate prognosis, with 5-year DFS rate of 66.6%. **Conclusion:** : SHT of TNBC encompasses heterogeneous malignancies with distinct behaviors. Lobular and metaplastic carcinomas showed high aggressiveness and poor treatment response, while medullary pattern and apocrine carcinomas had favorable outcomes. Treatment strategies focus on molecular features of each of these diseases are warranted.

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Introduction

Triple-negative breast cancer (TNBC) comprises 10 to 15% of breast cancer cases and its treatment still represents a key challenge[1,2]. Although TNBC is usually approached as a single disease, this group encompasses extremely heterogeneous diseases that differ in several aspects, such as epidemiology, histology, and gene expression, and consequently presents different clinical behavior, response to treatment, and survival[3,4]. Breast carcinoma of no-special type (or ductal breast carcinoma) is the most common histology, but about 25% of the breast carcinomas are special histological types[5].

To illustrate the diversity of TNBC special histological types, this group includes aggressive diseases with high proliferation index such as metaplastic and lobular carcinomas, as well as more indolent diseases with low proliferation index such as apocrine carcinomas[6].

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While metaplastic carcinomas are frequently chemoresistant and have a poor prognosis, medullary pattern carcinomas usually have a great response to treatment[7]. Nevertheless, since each of the TNBC special histologies is extremely rare and still poorly understood, they are often treated in the same way as the TNBC of no special type, without taking into account the differences between them.

In this study, we retrospectively selected special histologies of TNBC, including metaplastic, lobular, medullary, adenoid cystic, papillary, and apocrine carcinomas. Our objective was to assess the epidemiology, clinical behavior, and response to treatment of the TNBC special histological types.

Methods

Study design and participants

This retrospective cohort included patients with special histological types of triple-negative breast cancer treated from 2009 to 2020 at the Instituto do Câncer do Estado de São Paulo (ICESP, São Paulo, Brazil). ICESP is a tertiary cancer center that assists over 10,000 new cancer cases per year. Patients included had histologically confirmed triple-negative breast cancer with one of the following histological types: metaplastic, lobular, medullary, adenoid cystic, or apocrine. Breast cancer was considered triple-negative if estrogen receptor and progesterone receptor expression was lower than 1% and HER2 (Human Epidermal Growth Factor Receptor 2) was not amplified (HER2 score lower than 3+ in immunohistochemistry or negative in situ hybridization). Patients with any disease stage were included. Non-epithelial breast malignancies, such as sarcomas, phyllodes tumors, or lymphomas were not included.

The study endpoints were the description of clinical and pathological characteristics, pathologic complete response rate of patients treated with neoadjuvant chemotherapy, disease-free survival (DFS) for early breast cancer, progression-free survival (PFS) for advanced breast cancer, and overall survival (OS). Response to neoadjuvant chemotherapy was based on physical exam, breast image (mammogram, ultrasound and/or magnetic resonance imaging) and pathology results. Pathologic complete response was defined as the absence of residual invasive disease in the breast or axillary lymph nodes after neoadjuvant chemotherapy. Electronic records were reviewed for data collection. Clinical and demographic data evaluated comprised age, race, body mass index, personal and family history of cancer, disease stage, tumor grade, and Ki67 index. The treatment received and oncologic outcomes were revised and detailed.

The data were collected using electronic case report forms (RedCap®). The study was approved by the Local Ethics Committee.

Statistical analysis

Patients' characteristics and treatments received were tabulated and compared. Continuous variables were presented using median and range and compared between groups using one-way ANOVA. Categorical data were presented using absolute and relative frequencies and compared using Fisher exact test.

Survival analyses were estimated by the Kaplan-Meier method, with the use of the log-rank test to compare the survival curves. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). DFS was estimated from the date of diagnosis until the date of disease recurrence (local or distant recurrence) or death. PFS was estimated from the date of initiation of first-line chemotherapy until disease progression or death. OS was the time from the date of breast cancer diagnosis or the date of diagnosis of advanced disease for patients with advanced disease (at diagnosis or after recurrence) to the date of death from any cause. Patients without the events were censored at the date of the last follow-up.

The Stata software version 15.1 (StataCorp, Texas, USA) was used for the statistical analysis. P-values lower than 0.05 were considered statistically significant.

Results

Patients' characteristics

A total of 132 women with special histological types of triple-negative breast cancer were evaluated. The most common histology was metaplastic, with 71 cases. Others were medullary (n=14), lobular (n=12), adenoid cystic (n=12), apocrine (n=10). Thirteen patients had other histological types (clear cell, papillary, secretory, and squamous cell carcinoma) and were not evaluated separately due to the small number of patients in each group. Median follow-up was 42.4 months.

Clinical and pathological features differed importantly according to the special histological type (Table 1). Patients with metaplastic, medullary, and adenoid cystic carcinomas had younger median ages (51 to 53 years), while those with apocrine carcinomas were older (median age of 66 years) (P=0.009). More advanced disease stages were observed in metaplastic, apocrine, and lobular carcinomas, with 47 to 58% of stage III-IV disease. Otherwise, medullary and adenoid cystic carcinomas presented with earlier disease stages (57% and 75% were stage I-II). Lobular, metaplastic, and medullary carcinomas had higher tumor grades (66 to 85% of grade 3 tumors) and Ki67 index (median of 55 to 70%). Apocrine and adenoid cystic carcinomas had lower grades (70 and 83% of grade 1-2 tumors) and Ki67 index (median of 20% and 22.5%) (P<0.001 for both grade and Ki67 index).

Eight-five patients had the HER2 score detailed, and 85.9% of them were HER2 zero in immunohistochemistry. The HER2 zero score was the most common among the different subtypes, with the exception of apocrine carcinomas (Table 2). Among the apocrine carcinomas, 8 patients had HER2 score detailed; half of them (n=4) would be considered HER2-low, with two HER2 1+ and two HER2 2+ with negative in situ hybridization.

Outcomes – early breast cancer

Among 118 patients who presented with early breast cancer at diagnosis, 51 received neoadjuvant chemotherapy and 44 received adjuvant chemotherapy. Ninety-two percent of the patients treated with neoadjuvant chemotherapy and 68% of those treated with adjuvant chemotherapy received a regimen based on anthracyclines and taxanes.

Diverse disease behaviors and responses to therapy were observed depending on the special histological type. All patients with medullary carcinomas who received neoadjuvant chemotherapy achieved a pathologic complete response (n=7/7, 100%) compared

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Table 1 Clinical and pathological characteristics of the patients with special histological types of triple-negative breast cancer. Abbreviations: AC, adenoid cystic; IHC, immunohistochemistry; ISH, in situ hybridization.

	Metaplastic (n=71)	Medullary (n=14)	Lobular (n=12)	AC (n=12)	Apocrine (n=10)	P-Value
Age (median, range)	51 (22 – 83)	53 (34 – 74)	56 (28 – 84)	53 (40 – 78)	66 (46 – 90)	0.009
Stage at diagnosis (n, %)						0.205
I-II	34 (47.8%)	8 (57.1%)	5 (41.6%)	9 (75%)	5 (50%)	
III	30 (42.2%)	5 (35.7%)	5 (41.6%)	1 (8.3%)	4 (40%)	
IV	4 (5.6%)	1 (7.1%)	2 (16.6%)	1 (8.3%)	1 (10%)	
Grade (n, %)						<0.001
1	0 (0%)	0 (0%)	1 (8.3%)	4 (33.3%)	1 (10%)	
2	16 (22.5%)	1 (7.1%)	3 (25%)	6 (50%)	6 (60%)	
3	53 (74.6%)	12 (85.7%)	8 (66.6%)	2 (16.6%)	3 (30%)	
Ki67, % (median, range)	70 (20 – 100)	55 (5 – 95)	65 (6 – 90)	22.5 (10 – 70)	20 (5 – 70)	<0.001
HER2 score						0.101*
IHQ 0+	43 (60.6%)	3 (21.4%)	8 (66.7%)	8 (66.7%)	4 (40%)	
IHQ 1+	5 (7%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)	
IHQ 2+ with negative ISH	1 (1.4%)	0 (0%)	1 (8.3%)	0 (0%)	2 (20%)	
Negative, not detailed	22 (31%)	11 (78.6%)	3 (25%)	4 (33.3%)	2 (20%)	
Metaplastic subtype						
Adenosquamous	3 (4.2%)					
Squamous cell	18 (25.3%)					
Spindle cell	4 (5.6%)					
Mesenchymal differentiation	16 (22.5%)	-	-	-	-	
Matrix producing	18 (25.3%)					
Mixed	7 (9.8%)					
Other	2 (2.8%)					
Not available	3 (4.2%)					
AC subtype						
Classic				2 (16.7%)		
Solid/ Basaloid	-	-	-	3 (25%)		
Other				2 (16.7%)		
Not available				5 (41.7%)		

* Fisher's exact test, evaluating only the patients who had the HER2 score detailed.

to none of those with adenoid cystic (n=0/3, 0%) or apocrine (n=0/2, 0%) tumors. Pathologic complete response rates were 10.3% (n=3/29) for metaplastic and 33.3% (n=2/6) for lobular carcinomas. The presence of pathologic complete response was a favorable prognostic factor, with a 5-year DFS of 100% among patients with pathologic complete response compared to 48.6% among those with residual disease after neoadjuvant chemotherapy (P=0.003). Figure 1 shows the Kaplan-Meier curves for DFS of patients treated with neoadjuvant chemotherapy according to the pathologic response.

The 5-year DFS rates were numerically lower among patients with metaplastic and lobular carcinomas (56% and 51.4%). The 5-year DFS rates were 66.6%, 92.8%, and 83.3% for those with adenoid cystic, medullary, and apocrine tumors (P log-rank =0.074), respectivelly. The OS for early disease followed this same pattern, with numerically lower 5-year OS rates for metaplastic (63.3%) and lobular (64.2%) carcinomas.

Figure 2 illustrates the Kaplan-Meier curves for DFS and OS according to the special histological type. The oncologic outcomes of the special histological types of triple-negative breast cancer are summarized in Table 2.

Outcomes – advanced breast cancer

Forty-three patients had metastatic disease at diagnosis (n=16) or after disease recurrence (n=32). The most common first-line chemotherapy regimens were platinum-doublets (n=16, 37%), taxanes (n=10, 23%), and anthracyclines (n=7, 16%) (Table 2).

Due to the small sample sizes of the other groups, the oncologic outcomes for advanced breast cancer were evaluated only for metaplastic carcinomas. Median PFS of patients with metaplastic carcinoma after initiation of first-line chemotherapy was 4.3 months (Figure 3A). Median PFS was 5.4 months for patients who received first-line platinum regimens compared to 4.3 months for those treated with other regimens (HR 0.76, 95% CI 0.31 – 1.86, P=0.556). Median OS after the diagnosis of advanced disease was 13.3 months (Figure 3B).

Discussion

The present study highlights the high heterogeneity of the special histological types of TNBC and provides further data on each type's behavior. In our cohort, most patients had localized disease at diagnosis (89%). Metaplastic carcinomas were the most frequent special histology. These tumors are characterized by the differen-

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Table 2 Treatment received and outcomes of patients with special histological types of triple-negative breast cancer. Abbreviations: AC, adenoid cystic; NCT, neoadjuvant chemotherapy; CT, chemotherapy; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; mo, months; NA, not applicable.

Early disease	Metaplastic (n=64)	Medullary (n=14)	Lobular (n=10)	AC (n=11)	Apocrine (n=9)	P-Value
NCT, n (%)	29 (45.3%)	7 (50%)	6 (60%)	3 (27.3%)	2 (22.2%)	-
Response to NCT, n (%)						<0.001
Complete response	3 (10.3%)	7 (100%)	2 (33.3%)	0 (0%)	0 (0%)	
Partial response	15 (51.7%)	0 (0%)	1 (16.7%)	2 (66.6%)	0 (0%)	
Stable disease	4 (13.8%)	0 (0%)	0 (0%)	1 (33.3%)	2 (100%)	
Progressive disease	6 (20.7%)	0 (0%)	1 (16,7%)	0 (0%)	0 (0%)	
NA	1 (3.4%)	0 (0%)	2 (33.3%)	0 (0%)	0 (0%)	
Type of surgery, n (%)						0.002
Mastectomy	44 (68.7%)	3 (21.4%)	6 (60%)	3 (27.3%)	4 (44.4%)	
Conservative	17 (26.6%)	10 (71.4%)	2 (20%)	8 (72.7%)	5 (55.6%)	
No surgery	1 (1.6%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	
NA	2 (3.12%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	
Radiation therapy						0.962
Yes	46 (71.9%)	11 (78.6%)	7 (70%)	9 (81.8%)	7 (77.8%)	
No	15 (23.4%)	3 (21.4%)	2 (20%)	2 (18.2%)	2 (22.2%)	
NA/ Not applicable	3 (4.7%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	
Disease recurrence, n (%)	21 (32.8%)	1 (7.1%)	3 (30%)	3 (27.3%)	0 (0%)	0.100
Sites of recurrence						0.358
Local only	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	
Distant only	14 (21.9%)	1 (7.1%)	2 (20%)	2 (18.2%)	0 (0%)	
Both	7 (10.9%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	
Sites of distant recurrence						
1	1 (1.6%)	1 (7.1%)	1 (10%)	2 (18.2%)	0 (0%)	
2	15 (51.7%)	0 (0%)	1 (10%)	2 (18.2%)	0 (0%)	
3	2 (3.12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
4	4 (13.8%)	1 (7.1%)	1 (10%)	1 (9.1%)	0 (0%)	-
5	6 (20.7%)	0 (0%)	2 (20%)	1 (9.1%)	0 (0%)	
6	4 (13.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
7	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	
5y-DFS rates, % (95% CI)	56.0 (41.0 – 68.6)	92.8 (59.0 – 98.9)	51.4 (16 – 78.5)	66.6 (28.1 – 87.8)	83.3 (27.3 – 97.4)	0.074
5y-OS rates, % (95% CI)	63.3 (47.9 – 75.3)	92.3 (56.6 – 98.8)	64.2 (24.4 – 87)	88.8 (43.3 – 98.3)	83.3 (27.3 – 97.4)	0.142
Advanced disease	**(n=28)**	**(n=1)**	**(n=4)**	**(n=4)**	**(n=1)**	
1st line CT (n, %)						0.206
Platinum-based	14 (58.3%)	1 (100%)	0 (0%)	1 (100%)	NA	
Taxane	6 (25%)	0 (0%)	2 (100%)	0 (0%)		
Anthracycline-based	6 (25%)	0 (0%)	0 (0%)	0 (0%)		
Other	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)		
Median PFS, months	4.3 mo	NA	NA	NA	NA	-
Median OS, months	13.3 mo	NA	NA	NA	NA	-

tiation of the neoplastic epithelium into squamous cells and/or elements with mesenchymal characteristics, including spindle cells, chondroids, bone, rhabdomyoids, among others[5]. They are usually triple-negative and express keratins 5/6 and 14 and EGFR. Its incidence ranges from 0.2 to 1% of all invasive breast cancers. Compared with non-special type carcinoma, metaplastic carcinomas present as larger tumors at diagnosis, with less lymph node involvement and higher histological grade, as observed in the present study[8].

Despite being an aggressive and fast-growing disease, most cases of metaplastic TNBC had localized disease at the time of diagnosis (89%) in our cohort. Twenty-nine patients received neoadjuvant chemotherapy, of which 62% (n = 18) had a response; but only 3 achieved a pathologic complete response (10.3%). Six patients (20.7%) experienced disease progression during neoadjuvant chemotherapy. These results are in accordance with previous literature showing a pathologic complete response of 10 - 17% among patients with metaplastic carcinomas treated with neoadju-

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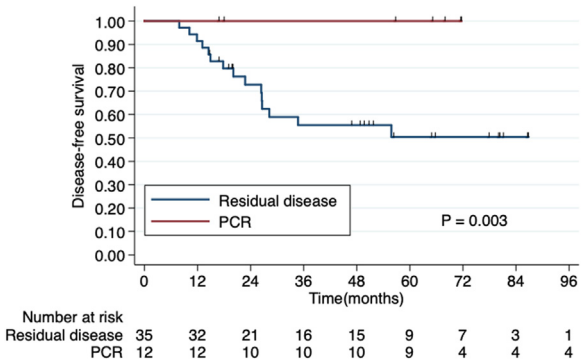
Figure 1 Disease-free survival of patients with special histologic subtypes of triple-negative breast cancer treated with neoadjuvant chemotherapy according to the pathologic response. Abbreviations: PCR, pathologic complete response.



vant chemotherapy[8-11]. In addition, recurrence rates were high, with a 5-year DFS of 56%. Based on the literature results, many physicians prefer not to offer neoadjuvant treatment for this group of patients. However, we believe that for a very aggressive disease as metaplastic breast cancer, an overall response rate above 60% justifies prospective studies for clarifying the benefits of this approach and, until we have these results, patients should not be generally deprived of neoadjuvant treatment.

Facing the low sensitivity to standard antineoplastic treatments and the poor prognosis of metaplastic carcinomas, the development of better personalized therapies is urgently needed. The broadening of next-generation sequencing is contributing to the comprehension of molecular features of special histologies. Regarding metaplastic carcinomas, a high frequency of p53 and PIK3CA mutations has been described[12,13]. Thus, drugs targeting the PI3K/AKT/mTOR pathway represent an interesting potential therapy to be investigated. Results from phase 1 trials investigating the mTOR inhibitors everolimus and temsirolimus for advanced metaplastic breast carcinomas have been reported. The addition of the mTOR inhibitor to bevacizumab and liposomal doxorubicin achieved response rates of 21 to 42%[14,15], and a phase II trial is currently ongoing (NCT02456857).

Immune checkpoint inhibitors are another promising treatment possibility. Phase 3 trials demonstrated the efficacy of the PD-1 inhibitor pembrolizumab for early and advanced TNBC of no-special type, while its activity for special types still requires further investigation. Biomarkers that potentially predict response to immunotherapy have been frequently observed in metaplastic carcinomas. Around 50 to 70% of metaplastic carcinomas present PD-L1 expression, a proportion higher than that observed in TNBC of no-special type[16-20]. Tumor-infiltrating lymphocytes (TILs) have also been frequently observed[19,20]. On the other hand, metaplastic carcinomas are usually microsatellite stable, and their tumor mutational burden (TMB) is usually low[20]. To date, a few case reports have described durable responses to immune checkpoint inhibitors in addition to chemotherapy for patients with metaplastic carcinomas[21,22].

Lobular TNBC also presented a poor prognosis, similar to metaplastic carcinomas, with a 5-year DFS of 51.4% for patients with early disease. Invasive lobular carcinoma is the most common of the special types, accounting for up to 15% of all breast cancer cases[5]. However, classic lobular carcinomas are characterized by a lack of E-cadherin and a predominantly luminal A molecular pattern. In contrast, the triple-negative variant is a rare and aggressive disease[23]. According to Lehmann's refining classification, lobular TNBC usually have a luminal androgen receptor (LAR) subtype, characterized by luminal gene expression and driven by the androgen receptor (AR)[3]. Echavarria et al showed that LAR tumors have the lowest pathologic complete response rates after neoadjuvant chemotherapy[4]. The lobular TNBC chemoresistance and the possible driven role of the AR pathway lead to the rationale for investigating anti-androgen therapies for this disease[4]. Nevertheless, studies evaluating these agents for TNBC so far did not specify the histological type[24-26].

Apocrine TNBC are also known for the frequent expression of AR receptor[27], but unlike lobular, they seem to have a better prognosis. Nevertheless, considering the rarity of the disease, its prognosis is still a matter of debate. Much rarer than its peers, apocrine TNBC represents around 0.4 - 4%, and data about surveillance are imprecise[28]. Apocrine differentiation leading to metaplasia and carcinoma is an accepted theory for the development of these tumors[29]. As well as metaplastic carcinomas, apocrine TNBC presents increased rates of PIK3CA, TP53, and MYC mutations[7]. Unlike metaplastic or lobular TNBC, however, our results points to a good prognosis of apocrine carcinomas[29]. No disease recurrence was observed among patients treated for early disease. The only DFS event that occurred was a death not related to apocrine carcinoma. Nevertheless, the response to chemotherapy was also poor. Only two cases were treated with neoadjuvant chemotherapy, both presenting stable disease. Sun et al published a cohort of 18 cases with genomic analysis, and describe 17 of them having at least one actionable alteration, raising the interest in the potential of targeted therapies[30]. Androgen deprivation led to disease control for one year in a rare case report of metastatic apocrine breast cancer[31]. Regarding the molecu-

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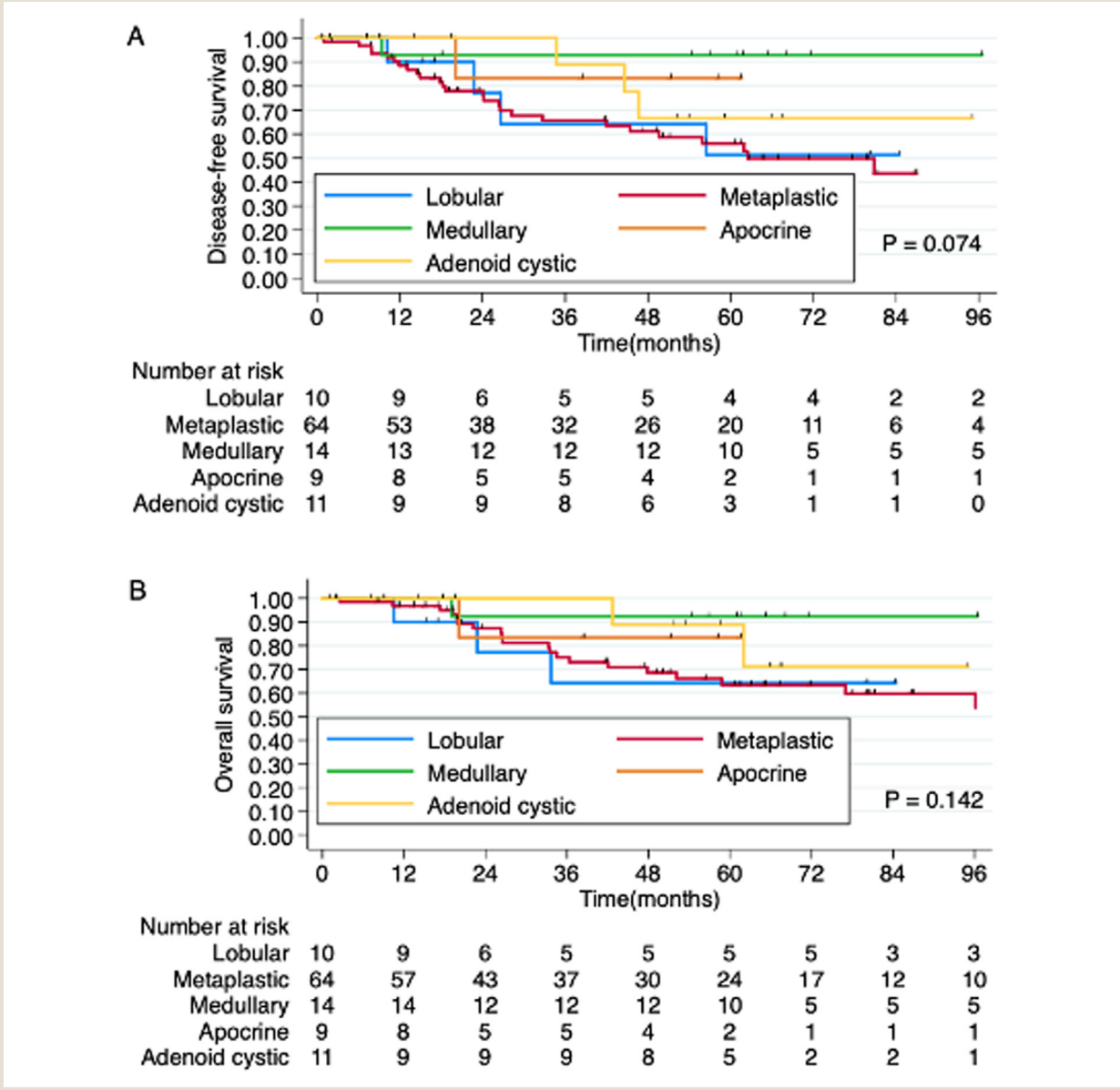
Figure 2 Disease-free survival (A) and overall survival (B) of patients with triple-negative early breast cancer according to the special histologic subtype.



lar intrinsic subtypes, the molecular apocrine-like tumors have been associated with poor prognosis. Among patients included in the EORTC10994 study, 93 had a molecular apocrine subtype, and the 5-year recurrence-free survival was 59.2%. Most of them had a ductal histology[32].

Cystic adenoid TNBC correspond to about 0.1 - 1% of breast cancers[33]. The biphasic pattern of myoepithelial and epithelial cells suggests cystic adenoid TNBC origins from ductal epithelium[33]. They usually occur in postmenopausal women between the fifth and sixth decades of life[34,35], and despite typically triple-negative phenotype, these tumors usually have a very good prognosis, with rare cases of metastasis in previous literature[33-36]. In our study, however, we identified 4 patients with metastatic cystic adenoid carcinoma. Treatment is not consensual[34,35], and considering its rarity, little is known about the role of systemic treatment. Our results suggest some activity of cytotoxic chemotherapy, since three patients received neoadjuvant chemotherapy, with two of them presenting a partial response.

Finally, medullary pattern of non-special type invasive carcinoma was the second most common histology in our sample, comprising 14 cases. Medullary pattern was previously described as medullary carcinoma, atypical medullary carcinoma or carcinoma with medullary features, representing less than 1% of breast cancer cases. These tumors were recently sub-classified as a special

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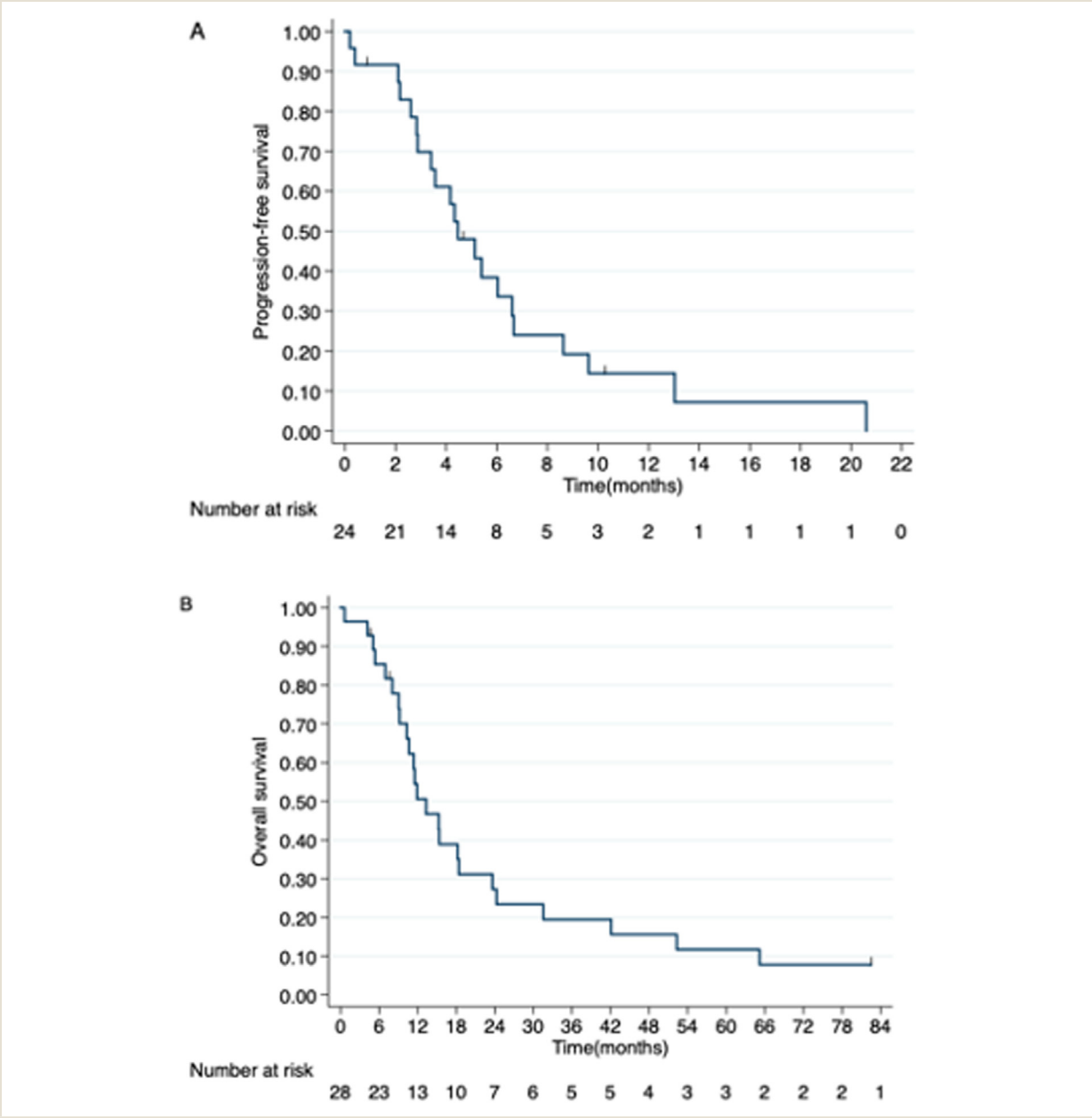
Figure 3 Progression-free survival (3A) after first-line chemotherapy initiation and overall survival (3B) after diagnosis of advanced disease of patients with metaplastic breast carcinoma.



pattern of invasive carcinoma among the non-special type[5]. Actually, medullary pattern represents a spectrum of diseases that has as its hallmark an immune-enriched microenvironment. They are usually triple-negative high-grade tumors as observed in our cohort, in which most of these tumors were grade 3 (85.7%), with a median Ki67 index of 55[5]. Despite presenting histological characteristics that suggest an aggressive disease, medullary pattern carcinomas have a better prognosis when compared to invasive carcinomas of no special type. This fact is attributed to the presence of a rich infiltrate of tumor-infiltrating lymphocytes (TIL), frequently observed in these tumors. Indeed, our results showed a pathologic complete response rate of 100% among the 7 patients who received neoadjuvant chemotherapy.

Conclusion

Our data confirm that TNBC have diverse behavior, response to treatment, and survival according to histological type. Lobular and metaplastic TNBC are more aggressive diseases, with many patients experiencing disease progression during neoadjuvant chemotherapy or recurrence after treatment for early disease. Medullary pattern

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and apocrine TNBC, otherwise, had much better outcomes. Despite the controversy regarding the benefits of neoadjuvant treatment for metaplastic TNBC, we believe that neoadjuvant treatment could be offered for these patients, especially if upfront surgery is not readily available. Molecular studies are warranted to further characterize each of the diseases and guide the development of better therapies.

Clinical Practice Points

- Due to the rarity of special histological types of triple-negative breast cancer (TNBC), many knowledge gaps still need to be clarified about these diseases. Treatment standards that are established for breast carcinoma of no special type frequently do not apply properly for the special types. Each special histological type seems to have particularities regarding the molecular background and disease behavior. Consequently, responses to treatment strategies can be highly distinct. Our results showed that metaplastic and lobular TNBC have a high aggressiveness, and response to cytotoxic chemotherapy is poor. On the other hand, medullary pattern carcinomas had a pathologic complete response rate of 100% after neoadjuvant chemotherapy. Although no benefit was observed with chemotherapy for apocrine carcinomas, patients with these tumors had favorable outcomes. Adenoid cystic carcinomas had an intermediate prognosis in our cohort. Additional studies focusing on molecular features of the special histological types of TNBC are warranted to guide the rational development of better treatment strategies.

Disclosures

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