



## Comparison of Rare Types of Breast Cancer

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### Authors' contributions

This work was carried out in collaboration among all authors. Author OE critical revision, drafting and writing article. Author AP conception and interpretation of data. Author KY design and literature research. Author UT interpretation, for critically important intellectual content. Author OI approved of the final version to be submitted. All authors read and approved the final manuscript.

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## ABSTRACT

**Aims:** Mucinous, medullary, and papillary carcinomas are rarely encountered types of breast cancer. This study aims to contribute to the literature by comparing the clinical and prognostic features and treatment alternatives of rare breast carcinomas.

**Study Design:** Thirty-four patients with rare breast cancer out of a total of 1368 patients who underwent surgery for breast cancer in our clinic between January 2011 and December 2020 were included in the study.

**Methodology:** The patients were assigned into three groups, i.e., medullary carcinoma group (Group 1), mucinous carcinoma group (Group 2) and papillary carcinoma group (Group 3). Demographic and clinical features, treatment modalities used, surgical approaches, pathological features of tumors and survival were compared between the groups.

**Results:** Thirty-four patients were included in the study. The mean age of the patients in Group 3 was higher, though it was not statistically significant. Modified radical mastectomy was more frequently performed in all the groups. The number of the lymph nodes removed through axillary

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dissections and the number of the positive lymph nodes were similar in all the groups. The tumors in all the groups were also of comparable sizes (30 mm in Group 1, 42.5 mm in Group 2 and 30 mm in Group 3;  $p:0.464$ ). Estrogen receptors were negative in a significantly higher rate of Group 1 (66.7% of Group 1,  $p<0,001$ ). A significantly higher rate of Group 1 received postoperative chemotherapy (93,3% of Group 1,  $p:0.001$ ), but the rate of the patients receiving hormonotherapy in this group was significantly lower (26.7% of Group,  $p<0,001$ ). The patients with medullary cancer had significantly longer survival than those with mucinous cancer and those with papillary cancer (76.2 in Group 1, 54.5 in Group 2 and 58.4 in Group 3;  $p:0.005$ ).

**Conclusion:** While rare subtypes of breast carcinoma did not affect opting for surgical treatment, selection of oncological therapy was affected depending on the hormone receptor status of these tumors. The long-term survival differed between rare breast tumors. In view of the unique clinical pictures of the tumors, the patients should be evaluated individually, and the evaluation should be associated with the evidence-based principles available for more common breast carcinomas.

**Keywords:** Breast cancer; medullary carcinoma; mucinous carcinoma; papillary carcinoma.

## ABBREVIATIONS

WHO : World Health Organization  
 RNA : Ribonucleic Acid  
 SLNB : Sentinel Lymph Node Biopsies  
 ALND : Axillary Lymph Node Dissection  
 ER : Estrogen Receptor  
 PR : Progesterone Receptor  
 HER2 : Human Epidermal Growth Factor Receptor 2  
 IHC : Immunohistochemical Analysis  
 NOS : No Special Type  
 DCIS : Ductal Carcinoma In-situ

## 1. INTRODUCTION

Breast cancer is the most frequent type of cancer in women throughout the world. Its incidence has increased over time and it is the second most frequent cause of death among women following lung cancer [1-5]. The incidence of breast cancer in Turkish women was 43,8 every 100.000 women in 2015 and increased to 45,6 in 2018. As in the rest of the world, one of every four women diagnosed as cancer in Turkey has breast cancer (24,4%). The mortality from breast cancer in 2018 was reported to be 10,5% [6,7].

Breast cancer treatment requires a multidisciplinary team including a radiologist, breast surgeon, hepatologist, medical oncologist and radiation oncologist. This team work creates a great effect on the prognosis of breast cancer.

The goal of cancer classification is to make an accurate diagnosis of the disease and to predict tumor behavior to facilitate decision making for oncological treatment. It is important to determine the carcinomas not needing

aggressive treatment, unresponsive to treatment and requiring aggressive treatment [3].

There has been a widespread insight into the heterogeneity of tumors in recent years. At present, there is greater emphasis on histological and molecular profiles. Effects of different profiles on prognosis and treatment have been reported [1].

Breast cancer is a heterogenous disease having many different biological subtypes displaying different phenotypical behavior and responding to treatment differently. Most of the breast tumors stem from the ductal epithelium of breasts, particularly terminal ductal-lobular unit. The most frequent histological type, also defined as invasive ductal carcinoma [no special type (NOS)], is infiltrative ductal carcinoma and accounts for 75% of the cases. The second most frequent histological type is invasive lobular carcinoma and accounts for 5-15% of the cases [8]. There is more than a dozen of variants less widespread but well-defined based on the classification by the World health Organization (WHO). According to this classification, breast carcinoma can be classified into 21 different histological types based on cellular morphology and growth and structure patterns [9].

There have been many studies on the effects of molecular subtypes of the tumors having the same pathological features on prognosis and treatment outcomes, which still attracts attention. At present, it has been shown that different microRNA expression characteristics of the same molecular subtypes of breast carcinomas are of prognostic significance [2,3,10,11,12,13].

The fact that most of the specific neoplasms are rare prevents performing large, randomized

studies to describe optimal treatment. Most of these cancers are defined in case reports and small patient series [14,15,16]. Despite increased evidence, biological behavior patterns of the rarely encountered histological subtypes of breast cancer are still unclear.

The aim of this study is to compare the clinical and prognostic features and treatment methods of rarely seen breast carcinomas in the patients treated and followed up in our clinic, and to contribute to the relevant literature.

## 2. PATIENTS AND METHODS

### 2.1 Patient Selection

After obtaining ethical approval for this retrospective study from Adana City Education and Research Hospital Ethical Board (IRB No. 10.03.2021/76/1327), the male and female patients having surgery for breast cancer in Adana City Education and Research Hospital between January 2011 and December 2020 were included in the study. The definitive diagnosis of the disease on pathological examination was retrospectively derived from the pathological examination reports.

The files of 1368 patients treated for breast cancer in our clinic were reviewed, and the patients diagnosed with invasive ductal carcinoma and invasive lobular carcinoma were not included into the study. The study comprised 51 patients with rare breast carcinomas. Of 51 patients, 17 were excluded from the study since the number of the patients with different types of breast cancer was insufficient for statistical analysis. Out of 17 patients, six had apocrine carcinoma, four had tubular carcinoma, two had metaplastic carcinoma, two had neuroendocrine tumor, two had pleomorphic carcinoma and one had squamous cell carcinoma. The remaining 34 patients were assigned into three groups. Group 1 included 15 patients with medullary carcinoma, Group 2 included 10 patients with mucinous carcinoma and Group 3 included 9 patients with papillary carcinoma.

The groups were compared in terms of demographic and clinical features, findings from imaging techniques, treatment modalities utilized, axillary dissection approach, postoperative complications, pathological features of the tumors, results of immunohistochemical examinations, recurrences, and survival.

Decisions about treatments of the patients were made by a multidisciplinary team involving

surgeons specializing in breast cancer, medical oncologists, and radiation oncologists. Advanced local tumors were given neoadjuvant treatment. Sentinel lymph node biopsies (SLNB) were performed by using a blue dye or radiocolloid injections. The patients were treated either with total mastectomy or breast preserving surgery.

When frozen section examinations of the sentinel lymph nodes (SLN) showed macrometastasis or micrometastasis, axillary lymph node dissection (ALND) was performed for level I and II lymph nodes (LN). Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were determined in resected primary tumors or core biopsy specimens. Allred scores were used to assess PR and ER status. Allred scores of three or more than 3 showed ER or PR positivity. HER2 expression was analyzed with immunohistochemical analysis (IHC). When it was difficult to make a decision based on HER2 on IHC, fluorescence in situ hybridization was utilized [17,18].

Data were obtained from the patient and hospital records. The latest data were gathered through death records or phone calls depending on survival status of the patients. The patients about whom sufficient clinical data were not available in the hospital records were not included into the study. Since the study had a retrospective design, informed consent was not obtained from the patients.

### 2.2 Statistical Analysis

Statistical analysis of obtained data was made with Statistical Package for the Social Sciences 23.0. Based on the standard deviation with the Rosner power analysis method, the sample size was 8 at 95% confidence interval due to independent samples and independent parameters. Data about categorical variables were expressed in numbers and percentages and data about continuous variables were presented by using mean and standard deviation (median and minimum and maximum values when necessary). Pearson Chi-square test and Fisher's exact test were adopted to compare categorical variables. Shapiro-Wilk test was utilized to determine whether the data were normally distributed. The Kruskal Wallis test was used to compare continuous variables when the data did not have a normal distribution. Analyses concerning survival were made with Kaplan-Meier and Log Rank tests. Statistical significance was set at 0.05 for all the analyses.

### 3. RESULTS

The study comprised 34 patients assigned into three groups: Group 1, including 15 patients with medullary carcinoma, Group 2, including 10 patients with mucinous carcinoma and Group 3, including 9 patients with papillary carcinoma. There was only one male patient in Group 3. The distribution of tumor locations in all the groups was homogenous. The mean age of the patients was higher in Group 3 without a significant difference (58 years in Group 1, 58 years in Group 2 and 65 years in Group 3;  $p:0.350$ ). The distribution of benign and malignant conditions on imaging techniques was also similar. Twenty-six-point-seven percent of Group 1 and 30% of Group 2 had neoadjuvant treatment, but none of the patients in Group 3 had neoadjuvant treatment. Demographic and clinical features of the patients are shown in Table 1.

The most frequent surgical technique utilized was modified radical mastectomy (66.7% of Group 1, 40% of Group 2 and 55.9% of Group 3;  $p:0.148$ ). There was not a significant difference in the number of the lymph nodes removed through axillary dissection and the number of the positive lymph nodes between the groups ( $p:0.093$  and  $p:0.710$  respectively). Table 1 presents data about surgical variables.

The tumor size was also similar in the groups (30 mm in Group 1, 42.5 mm in Group 2 and 30 mm in Group 3;  $p:0.464$ ). ER was negative in a significantly higher rate of Group 1 (66.7% of Group 1, 0% of Group 2 and 0% of Group 3;  $p<0.001$ ). Similarly, PR was negative in a significantly higher rate of Group 1 (66.7% of Group 1, 0% of Group 2 and 22.2% of Group 3;  $p:0.002$ ). The number of the triple-negative patients was significantly higher in Group 1 (40% of Group 1, 0% of Group 2 and 0% of Group 3;  $p = 0.010$ ). The tumor grade was higher in Group 1. In fact, 70% of the patients in Group 1 had grade 3 tumors ( $p:0.023$ ). There were no statistically significant differences between the groups in terms of pathological staging. Table 1 outlines pathological variables.

A significantly higher rate of Group 1 had postoperative chemotherapy (93,3% of Group 1, 30% of Group 2 and 88.9% of Group 3;  $p:0.001$ ), but a significantly lower rate of Group 1 had hormonotherapy (26.7% of Group 1, 100% of

Group 2 and 100% of Group 3;  $p<0.001$ ). Group 2 had a lower survival at the time of the study (93% of Group 1, 60% of Group 2 and 100% of Group 3;  $p:0.024$ ). Data collected during oncological follow-ups are shown in Table 2.

The medullary carcinoma group had a significantly higher survival than the mucinous carcinoma and papillary carcinoma groups (76.2% of Group 1, 54.5% of Group 2 and 58.4% of Group 3;  $p:0.005$ ). Table 3 and Fig. 1 demonstrate survival rates of the groups. The mucinous carcinoma group was found to experience recurrences earlier than the other groups; however, the difference was not significant.

### 4. DISCUSSION

Conventional classifications of breast carcinomas have been made based on their pathological features, evaluations of hormonal receptors on IHC analyses and HER2 in terms of their use and validity in clinical practice. They are inexpensive and practical to use routinely. Besides, pathological subtypes of breast cancer have been described. Pathological features of breast cancer play an important role in selection of surgical and oncological treatment modalities. In the present study, we retrospectively investigated clinicopathological features and survival outcomes of rarely encountered breast carcinomas.

Medullary breast carcinoma is a subtype accounting for less than 1% of all the invasive breast carcinomas and displaying a favorable prognosis in spite of its aggressive morphological features. The immunoprofile of medullary breast carcinoma is similar to that of triple-negative tumors without immunoreactivity for ER, PR, and HER-2 / neu oncogene [19]. Mucinous breast carcinoma is rarely seen in clinical practice and it is responsible for about 1-7% of all the invasive breast carcinomas. It appears in perimenopausal and postmenopausal age groups and its ten-year survival is around 90% [20].

Invasive papillary carcinoma is defined as having a papillary structure in more than 90% of its invasive component. The general incidence of invasive papillary carcinoma is low and accounts for less than 1-2% of all newly diagnosed invasive breast carcinomas [21].

Table 1. Demographic and surgical and pathological variables

	Medullary n (%)	Mucinous n (%)	Papillary n (%)	Total n (%)	P
<b>Gender</b>					
Female	15 (100)	10 (100)	8 (88,9)	33 (97,1)	0,239
Male	0 (0)	0 (0)	1 (11,1)	1 (2,9)	
<b>Laterality</b>					
Left	10 (66,7)	4 (40)	5 (55,6)	19 (55,9)	0,421
Right	5 (33,3)	6 (60)	4 (44,4)	15 (44,1)	
<b>Age (years) Median (Min-Max)</b>	58 (32-74)	58 (38-93)	65 (45-76)	59 (32-93)	0,350
<b>Neoadjuvant treatment</b>					
Yes	4 (26,7)	3 (30)	0 (0)	7 (20,6)	0,200
No	11 (73,3)	7 (70)	9 (100)	27 (79,4)	
<b>Surgery</b>					
Simple Mastectomy	0 (0)	1 (10)	1 (11,1)	2 (5,9)	0,581
Segmental Mastectomy	5 (33,3)	5 (50)	3 (33,3)	13 (38,2)	
Modified Radical Mastectomy	10 (66,7)	4 (40)	5 (55,6)	19 (55,9)	
<b>SLNB</b>	2 (13,3)	4 (40)	3 (33,3)	9 (26,5)	0,288
<b>The number of the lymph nodes removed through axillary dissection</b>	20 (10-44)	16 (10-32)	14,5 (11-20)	18 (10-44)	0,093
<b>The number of the positive lymph nodes</b>	0 (0-3)	0 (0-2)	0,5 (0-4)	0 (0-4)	0,710
<b>Tumor size (mm)</b>	30 (7-100)	42,5 (12-65)	30 (8-55)	32,5 (7-100)	0,464
<b>ER</b>					
Positive	5 (33,3)	10 (100)	9 (100)	24 (70,6)	<b>&lt;0,001</b>
Negative	10 (66,7)	0 (0)	0 (0)	10 (29,4)	
<b>PR</b>					
Positive	5 (33,3)	10 (100)	7 (77,8)	22 (64,7)	<b>0,002</b>
Negative	10 (66,7)	0 (0)	2 (22,2)	12 (35,3)	
<b>HER2</b>					
Positive	5 (33,3)	2 (20)	1 (11,1)	8 (23,5)	0,440
Negative	10 (66,7)	8 (80)	8 (88,9)	26 (76,5)	
<b>Triple-Negative</b>					
Yes	6 (40)	0	0	6 (17,6)	<b>0,010</b>
<b>DCIS</b>					

	<b>Medullary</b>	<b>Mucinous</b>	<b>Papillary</b>	<b>Total</b>	<b>P</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
Yes	3 (20)	3 (30)	4 (44,4)	10 (29,4)	0,445
No	12 (80)	7 (70)	5 (55,6)	24 (70,6)	
<b>Grade</b>					
1	0 (0)	1 (20)	2 (28,6)	3 (13,6)	<b>0,023</b>
2	3 (30)	4 (80)	4 (57,1)	11 (50,0)	
3	7 (70)	0 (0)	1 (14,3)	8 (36,4)	
<b>Stage</b>					
1	5 (33,3)	1 (10)	1 (11,1)	7 (20,6)	0,407
2	7 (46,7)	8 (80)	7 (77,8)	22 (64,7)	
3	3 (20)	1 (10)	1 (11,1)	5 (14,7)	

ER: estrogen receptor, PR: progesterone receptor; HER2: Human epidermal growth factor receptor 2, DCIS: ductal carcinoma in situ

**Table 2. Data collected during oncological follow-ups**

	<b>Medullary</b>	<b>Mucinous</b>	<b>Papillary</b>	<b>Total</b>	<b>P</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
<b>Chemotherapy</b>					
Yes	14 (93,3)	3 (30)	8 (88,9)	25 (73,5)	<b>0,001</b>
No	1 (6,7)	7 (70)	1 (11,1)	9 (26,5)	
<b>Radiotherapy</b>					
Yes	8 (53,3)	7 (70)	4 (44,4)	19 (55,9)	0,515
No	7 (46,7)	3 (30)	5 (55,6)	15 (44,1)	
<b>Hormonotherapy</b>					
Yes	4 (26,7)	10 (100)	9 (100)	23 (67,6)	<b>&lt;0,001</b>
No	11 (73,3)	0 (0)	0 (0)	11 (32,4)	
<b>Recurrences</b>					
Yes	1 (6,7)	3 (30)	1 (11,1)	5 (14,7)	0,255
No	14 (93,3)	7 (70)	8 (88,9)	29 (85,3)	
<b>Mortality</b>					
Yes	1 (6,7)	4 (40)	0 (0)	5 (14,7)	<b>0,024</b>
No	14 (93,3)	6 (60)	9 (100)	29 (85,3)	

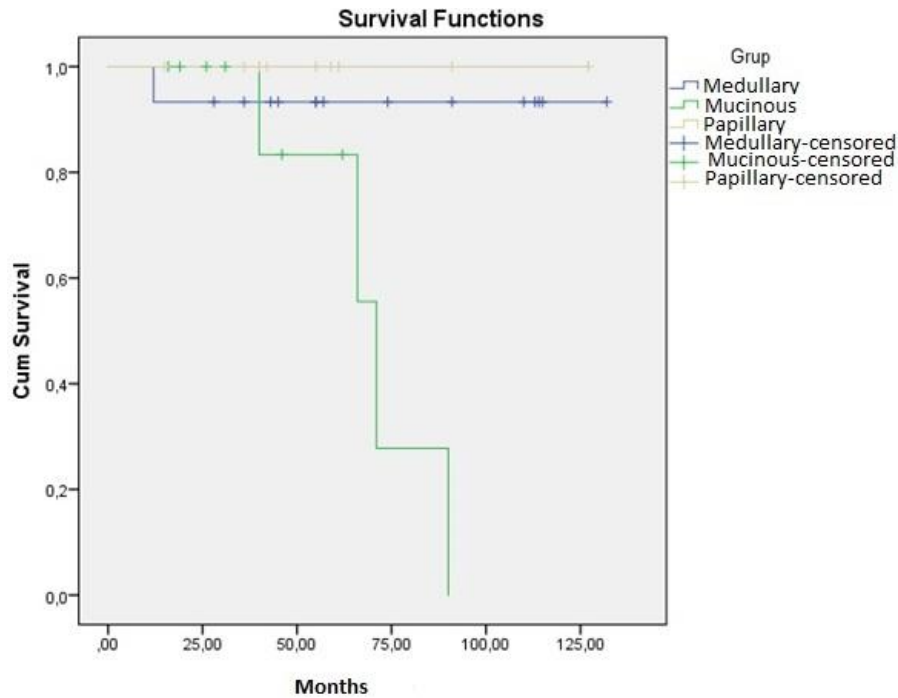


Fig. 1. Survival rates

Table 3. Duration of survival

Groups	Mean <sup>a</sup>				P
	Estimate	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Medullary	76,2	9,3	57,879	94,692	<b>0,005</b>
Mucinous	54,5	9,5	35,758	73,362	
Papillary	58,4	11,0	36,800	80,089	

In a series of 242863 breast cancer patients, Han reported that 230213 patients had DCIS and 12650 people had a rare breast carcinoma. The researcher also noted that rare breast tumors had a lower histological grade, smaller size, lower rate of lymph node involvement and lower rate of distant metastases and that although prognosis was poorer in metaplastic breast carcinoma, it was significantly better in apocrine, medullary, micropapillary and papillary breast carcinomas. In the same study while the proportion of triple-negative (TN) subtype was significantly higher in the patients with special breast cancer (TN, 16.2% vs. 12.7%,  $P < 0.0001$ ). The proportion of TN breast cancer was dramatically higher in adenoid cystic breast cancer (TN, 74.8% vs. 12.7%,  $P < 0.0001$ ), apocrine breast cancer (TN, 52.4% vs. 12.7%,  $P < 0.0001$ ), medullary breast cancer (TN, 57.3% vs. 12.7%,  $P < 0.0001$ ), and metaplastic breast cancer (TN, 68.6% vs. 12.7%,  $P < 0.0001$ ). In our

series, we found TN breast cancer only in the medullary carcinoma group. Regarding clinicopathological factors, special breast cancer tended to present less aggressive biological behaviors, which exhibited the relatively lower histological grade and TNM staging. In our series, there was no difference between the subtypes in terms of stage, and stages 1 and 2 were frequent. Findings from Han's study confirmed the clinicopathological and prognostic differences between histopathological subtypes [22].

Vo et al. evaluated long-term outcomes of breast preserving surgery for invasive ductal, medullary, mucinous, and tubular carcinomas and did not find a significant difference in local recurrence rates during a median follow-up of 10.6 years between four groups. Only the patients with tubular carcinoma had better five-year and ten-year survival rates ( $P .013$ ). They recommended that breast preserving surgery could be used

safely in rare histological types of breast carcinomas [23].

Gök et al. compared rare breast carcinomas, i.e., papillary, pure mucinous and tubular carcinomas and their subgroup analysis did not reveal a significant difference in demographic features, clinicopathological features, surgical treatment methods and oncological treatment choices [10].

In the current study, no significant relation was found between tumor types and age of patients, results of imaging methods, selected surgical method and axillary dissection approach. As expected, ER, PR and Cerb-2 were negative in a higher rate of the cases of medullary breast carcinoma and these cases had higher grade tumors. They were treated with chemotherapy regimens but were not given hormone therapy since hormone receptors were negative. As opposed to histopathological features, the cases of mucinous breast carcinoma had a lower survival and a higher death rate during the follow-up.

The limitations of the present study were its limited number of patients and retrospective nature. However, the results of the study still contribute to the relevant literature since comparative studies about the issue have had small sample sizes.

## 5. CONCLUSION

To conclude, whereas subtypes of rare breast carcinomas had no impact on the selection of surgical methods, they could be effective in oncological treatment methods depending on the hormone receptor status of these tumors. There were differences in long-term survival between rare breast cancer carcinomas. Time to recurrences was shorter in the cases of mucinous breast carcinoma. Large meta-analyses are needed to provide a better insight into differences in biological behavior between rare breast carcinomas.

## CONSENT

Written informed consent was obtained from all the patients.

## ETHICAL APPROVAL

This study is planned after the approval of Adana City Training and Research Hospital Ethical Committee.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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