Original Article

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Characteristics of Special Type Breast Tumors in Our Center

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ABSTRACT

Objective: Breast cancer is a heterogeneous disease with different histological types. Ductal breast cancer constitutes the vast majority of the breast cancers. However limited data are present in the rest of breast cancers called special or rare type breast cancers. Here in this study, we tried to describe the clinical features of special type breast cancers in our center.

Materials and Methods: Retrospective descriptive study was performed in Kocaeli University School of Medicine, Department of General Surgery between January 2000 and January 2016. Women diagnosed with primary breast cancer other than ductal carcinoma were included to the study. In total, 101 patients were evaluated according to histologic types, molecular types, Tumor Node Metastasis (TNM) stages, and grades. Survival of the patients was also evaluated.

Results: Medullary and metaplastic types showed basal type; tubular, mucinous, micropapillary carcinoma, cribriform, lobular and apocrine tumors showed luminal type molecular pattern. Neither the existence of ductal carcinoma nor any histologic types had any effects on survival. Apocrine tumors were presented in younger ages.

Conclusion: Histologic types of breast cancer are closely related with the molecular types of the breast cancer. Tumor size, grade, stage of the disease can show differences among histological types which might be due to the genetic background, late onset or limited number of patients. In order to achieve more significant results, multicenter national studies are needed.

Keywords: Breast carcinoma, histological tumor type, molecular classification, rare tumors

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Introduction

Breast cancer, which is the most diagnosed cancer among women, is a heterogeneous disease, consisting of numerous, distinct clinical and biological features. Breast cancer is a collection of different diseases with different risk factors, clinical presentations, pathological features, and treatment responses and outcomes. In order to classify different breast cancers, several parameters have been used. Tumor grade, Tumor Node Metastasis (TNM) staging, histological classification, existence of axillary lymph node metastasis, immunohistochemical biomarker characterization, and molecular profiling are the parameters used for classification of breast tumors (1).

Histological type is derived from the growth pattern of the breast tumors. Specific morphological and cytological patterns are associated with distinctive clinical presentations and/or outcomes (2). The most common type of breast cancer is an invasive ductal carcinoma (IDC). In the last version of the World Health Organization classification, at least 17 distinct histological special types have been recognised and specialized types account for up to 25% of all breast cancers (3). Special or rare breast tumor terminology was first described in the study of Weigelt B. et al. (2). Although new treatment protocols depend on molecular findings, histological groups still carry important clinical implications (3). As the prevalence of special type breast cancer is low, not as many studies are concerned with the clinical and molecular characteristics of special type breast cancer (4). In this study, we aimed to describe the clinical features of special type breast cancer in our center.

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Material and Method

This retrospective descriptive study was performed at Kocaeli University School of Medicine, Department of General Surgery between January 2000 and January 2016. The study was approved by local the ethics committee (KOU KAEK 2015/261). Patient information was collected from the hospital database and pathology reports. Pathology slides in which the pathology reports lacked the desired information were re-evaluated. Women diagnosed with primary breast cancer were collected from our data. As being a retrospective study, inform consent was not received from the patients. Patients with IDC, malign phyllodes, and sarcomas were excluded from the study. The remaining 101 patients were diagnosed with medullary, tubular, mucinous, metaplastic, micropapillary carcinoma, cribriform, lobular, and apocrine tumors. Patients' ages were obtained. Information about sides, sizes, axillary lymph node statutes, molecular types, stages, and cancer grades were collected. The presence of ductal carcinoma in situ (DCIS) in the breast tissue samples with the primary tumor was examined. Identified special type tumors were subgrouped into molecular subtypes according to the St. Gallen Consensus (5). According to the St Gallen Consensus, immunohystochemical analyses were performed in order to define the status of estrogen and progesterone receptors (ER and PR, respectively), human epidermal growth factor receptor 2 (HER-2), and the proliferation marker, Ki-67. Staining >10% for ER and PR are regarded as positive. Membranous uninterrupted staining of tumor cells with HER-2 >10% is regarded as positive. The set point for Ki-67 is accepted at >20%. The follow-up times and patient survival were recorded. Data were recorded in SPSS 15.00 (SPSS Inc. Chicago, IL, USA). The results were given by mean ± standard deviation. Comparison of molecular type and stages between histological types were performed by the chi-square Monte Carlo method. Comparisons of mean tumor size between groups were performed by analysis of variance (ANOVA). Comparisons of lymph node status between subgroups were performed by Chi-squared test. These comparisons, however, were formed between groups which had >5 patients. Patient survival was measured with the Kaplan-Meier test. p values <0.05 was accepted as significant.

Table 1. Characteristics of rare breast tumor types

	Medullary (n=12)	Tubular (n=5)	Mucinous (n=18)	Metaplastic (n=5)	Lobular (n=56)
Mean Age (Year)	56.5	59.8	58.9	56.8	53.9
Right/Left	8/4	2/3	5/13	1/4	33/23
Mean Tumor size*	3.7	1.5	3.8	3.9	4.3
Tumor size (cm)					
<2.0	1	4	3	1	8
2.0-4.9	6	1	12	3	28
≥5.0	5	0	3	1	20
Lymph node status					
Negative	5	4	12	4	21
Positive	7	1	6	1	35
Molecular type					
Luminal A	1	4	10	0	40
Luminal B	0	1	8	0	11
HER2/ER	2	0	0	0	1
Basal	9	0	0	5	4
Grade					
I	0	5	12	0	31
II	0	0	3	2	23
III	12	0	3	3	2
Stage					
I	1	4	5	1	8
II	10	1	9	3	19
III	1	0	4	1	29
IV	0	0	0	0	0
Existence of DCIS	0	4	2	2	120

*p=0.2 (ANOVA)
DCIS: ductal carcinoma in situ

Results

Of the eight histological types assessed, the characteristics of breast tumors were given in Table 1. There were no significant differences between the mean tumor size of histological types (p=0.2). When the tumor sizes were grouped according to T staging, there was a significant difference between T stages in different groups (p=0.019). It can, however, be seen that micropapillary carcinoma was more likely to be diagnosed with the tumors that were ≥5.0 cm while tubular carcinoma cases were more likely to be diagnosed when they were <2.0 cm. There were no significant differences between the groups according to the lymph node positivity (p=0.25). However medullary and micropapillary carcinoma cases also were more likely to be diagnosed with lymph node-positive disease. The number of patients with stage II medullary, mucinous carcinoma were significantly higher than the other stages (p=0.02). Rare breast tumors generally presented at stages I and II (20.7% and 54.5%, respectively). None of the patients presented at stage IV. There were no differences between right or left side tumors in rare breast tumors (p=0.54)

Table 1. (Continued)

	Micropapillary (n=3)	Cribriform (n=1)	Apocrine (n=1)	Total (n=101)
Mean Age (Year)	55.1	68.0	41.0	59.4
Right/Left	1/2	1/0	0/1	23/30
Mean Tumor size*	5.5	4.0	5.0	3.8
Tumor size (cm)				
<2.0	0	0	0	9 (17%)
2.0-4.9	0	1	0	28 (53%
≥5.0	3	0	1	16 (30%)
Lymph node status				
Negative	0	1	0	20 (37.7%)
Positive	3	0	1	33 (62.3%)
Molecular type				
Luminal A	3	1	1	31 (58.4%)
Luminal B	0	0	0	
HER2/ER	0	0	0	5 (9.4%)
Basal	0	0	0	17 (32.2%)
Grade				
I	0	1	0	30 (56.6%)
II	1	0	0	6 (11.3%)
III	2	0	1	17 (32.1%)
Stage				
I	0	0	0	11 (20.7%)
II	0	1	0	29 (54.7%)
III	3	0	1	13 (24.6%)
IV	0	0	0	0
Existence of DCIS	3	1	1	15 (28.3%)

*p=0.2 (ANOVA) DCIS: ductal carcinoma in situ

When the special type of breast tumors were evaluated according to the molecular types, all types expect medullary showed unique molecular patterns. Medullary type breast cancer showed 75% basal type tumors. Lobular breast tumors were mostly classified as luminal type (91.4%). Luminal type breast cancers included tubular, mucinous, micropapillary, lobular, cribriform, and apocrine tumors. Basal type breast tumors were medullary, lobular, and metaplastic. HER2 tumors were composed of medullary and lobular type breast tumors. This indicated that special type breast tumors have specific molecular patterns.

Existence of DCIS was significant in apocrine (100%), cribriform (100%), and tubular (80%) type breast tumors. However DCIS was not seen in medullary type tumors. Only 28% of the patients with rare breast tumors had DCIS (Table I). Although the numbers of patients were low, survival of the patients did not showed significant differences according to the tumor types or existence of DCIS (Figure 1) (p>0.05).

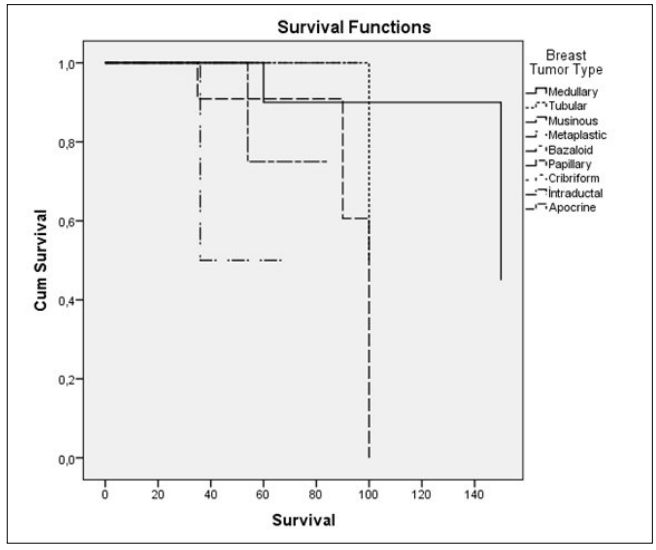

Figure 1. Survival of rare breast tumors

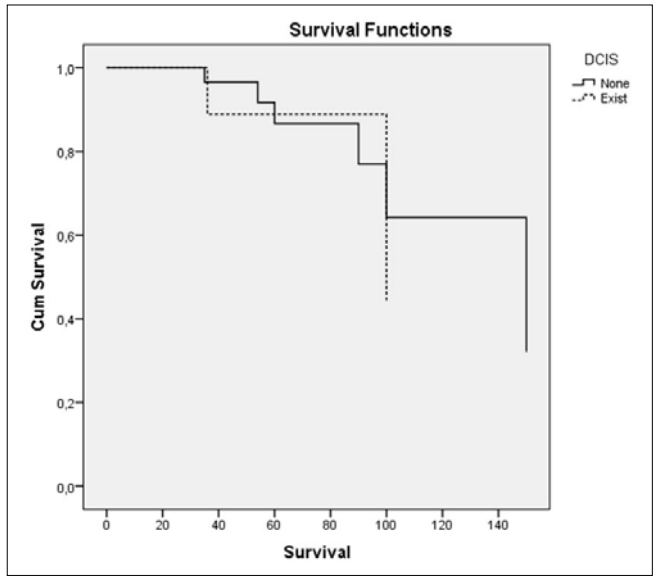

Figure 2. Survival of rare breast tumors according to existence of ductal carcinoma in situ

Low grade tumors were seen more frequently in tubular, mucinous, and cribriform cancers. On the other hand, high grade tumors were seen much more frequently in apocrine and metaplastic type tumors. Among the histological types, cribriform cases had the oldest age at diagnosis (68 years) and apocrine cases had the youngest age at diagnosis (41 years). The number of deaths during the follow-up of the patients was as follows: two for medullary, one for tubular, three for mucinous, and one for metaplastic. Survival rates are shown in Figure 2. Of note, net survival rate for lobular carcinoma was not achieved.

Discussion and Conclusion

This study determined the characteristic of special type breast tumors and showed that histological breast cancers have unique molecular types. Rare breast tumors are generally detected in early stages. Before interpreting the study results, it's important to acknowledge the study's limitations. Firstly, the number of cases was limited and statistical analysis could not be performed as desired in some comparisons. Pathological evaluations were not performed by one pathologist as the time period for this retrospective study covered 16 years. Finally, information about treatment and surgery were not given. However the results were sufficient enough to reach an outcome.

Previous studies that have explored age distribution of different histological types of breast cancer have shown that micropapillary and mucinous carcinomas tend to increase with age, whereas medullary carcinomas tend to decrease (6, 7). In our study, the mean age of patients with histological types of breast cancer were >55 years except in cases of apocrine carcinomas. The genetic background and low number of cases in our study might be the reason for the difference among those different types of carcinomas.

Medullary carcinoma includes breast tumors with medullary features and is less likely to present at an advanced age. Although one fourth of the medullary cancers are diagnosed in patients before 35 years, only 13% of them have Brest Cancer Susceptibility Gene 1(BRCA1) germline mutations (8). Gene expression analysis of medullary breast cancer has revealed upregulation of genes involved in Th1 immune cytokines and genes related to apoptosis. Conversely, genes associated with skeletal cell architecture are downregulated (9). These specific mutations, rather than Brest Cancer Susceptibility Gene (BRCA), have also led triple negative molecular features and expression of basal markers (1). Showing a high level of genomic instability and basal features, the presence of lymphocytic infiltrate and cell invasion-associated downregulated genes has led to high grade, but favorable, outcomes (10). Occurrence of host reactions is thought to be the mechanism for these favorable outcomes. As in the literature, our medullary carcinomas showed basal markers of high grade with early stages of the disease. Basal molecular types are mostly seen in medullary type breast cancers as mentioned in the literature. In the study of Chu Z. et al. (11), 44.4% of medullary type breast cancer patients were in the basal-like molecular group. However, our luminal type medullary cancer cases were more prevalent than those described in the literature. In the literature, the two year disease-free survival was reported at 79% for basal type medullary breast cancer (12). In our study, two cases which were basal-like died during the follow-up period. Molecular subtype is the most important factor affecting medullary prognosis has yet to be determined. Although the lymph Node (LN) metastasis in medullary cancer was found to be <30%, in our study LN metastasis was >50% (11).

Tubular carcinoma is more often seen in older patients and is generally detected in screening mammography as calcifications and small masses (1). Nearly one fifth of the patients with tubular breast carcinoma are multifocal. Only 10% of cases present with axillary metastasis. For this reason most of the patients present with early stages. In our study, the mean age of tubular carcinoma was 59.8 years, and 80% of cases had tumors <2 cm with a mean diameter of 1.5 cm, and 20% of cases had lymph node involvement. As in previous studies, tubular carcinomas present luminal type markers (9). DCIS involvement has been shown at 52% in previous studies, which was less than in our study (80%) (13). Tubular carcinoma was the breast tumor with the highest DCIS existence rate in our study.

Mucinous breast cancer are generally seen in patients >55 years. These tumors can present with different sizes ranging from 1 to 20 cm. Mucinous carcinomas are luminal type and usually present at an early stage and are often low histologic grade (14). Besides pure mucinous breast cancer, some types of mucinous carcinomas can contain neuroendocrine differentiation which shows invasive carcinoma features (9). In a detailed search, we found that three of our cases showed invasive forms. These three patients were in stage III with high grade tumors. For this reason, mucinous tumors should be carefully investigated as to whether there is neuroendocrine differentiation. Our results were similar with the previous studies (1, 4).

Metaplastic carcinomas have features of neoplastic cell differentiation into squamous cells and mesenchymal elements. Metaplastic carcinomas are generally large and display a basal-like phenotype (14, 15). These findings were similar to those in our study. Axillary lymph node metastases are less commonly seen but distant metastasis without lymph node metastasis can be seen. The reason for worsening prognosis of metaplastic carcinoma depends on the mutation of genes related to myoepithelial differentiation, Wnt signaling pathway genetic activation, BRCA1 DNA response pathway, and the phosphatase and tensin homolog and DNA topoisomerase 2-alpha genes (16, 17). These features cause the tumor to be more resistant to chemotherapy. The vast majority of metaplastic breast tumors are basal-like and have a worse patient prognosis than the triple negative infiltrating ductal carcinoma (18). Although worse prognosis were indicated in especially basal-like types, survival of histological groups did not showed any differences in our study. This may be related to the early stage of the metaplastic carcinomas or the genetic background of our cases.

Invasive micropapillary carcinoma is a special type of breast tumor composed of tumor cells arranged in morula-like cell clusters with lack of a fibrovascular core in the stromal spaces. This pattern can be seen in all areas or can be partially seen as a component of invasive ductal carcinoma. Existence of micropapillary patterns of at least 75% of the tumor is accepted as pure invasive micropapillary carcinoma (19). Micropapillary carcinomas are generally seen in postmenopausal women, and the mean age of the patients reported in the literature was given between 50 and 55 (20). Micropapillary carcinomas are often medium-high grade tumors. When compared to nonmicropapillary carcinoma, micropapillary carcinomas had more lymphovascular invasion, lymph node metastases, and invasion to perinodal fatty tissue infiltration (21). Most of the micropapillary carcinomas stained positive with ER and PR, but HER-2 positivity was seen in 4%–15% of the cases in the literature (22-24). The cases of the worst micropapillary carcinoma prognoses rather than ductal carcinomas depended on the genetic instability.

Apocrine carcinomas are special types of breast tumors which are composed of dark eosinophilic, granular, and vacuolated cytoplasms and significant nuclei. Apocrine features can be seen in many breast tumors, but apocrine carcinoma is applicable when the morphology is seen in every part or nearly every part of the tumor. Apocrine carcinoma constitutes 1%–4% of all breast tumors. It can be seen at all ages but is more prevalent in the postmenopausal period. Apocrine tumors are high grade tumors.

Lymphovascular invasion in apocrine tumors occurs much more than in infiltrating ductal carcinoma. Apocrine tumors are generally ER positive, and only half of them showed HER2 positivity (25). Only one case in our study showed HER2 and ER positivity. Apocrine tumors were reported in the study of Zhang et al. (26) in which apocrine breast tumors were associated with older age, lower ER and PR proportions, larger tumor size, higher grade, more positive LN, an aggressive stage, and higher HER2 amplification than seen in infiltrating ductal carcinomas.

Cribriform carcinomas are considered to belong a low-grade breast neoplasia family with small size and less frequent axillary LN metastases, higher ER and PR receptor positivity, and lower proliferation indices (27). The important feature of invasive cribriform breast cancer is the cribriform growth pattern that is used for differentiation from tubular carcinoma. Cases with a component of another carcinoma type accompanying cribriform pattern are regarded as mixed type invasive cribriform cancer and have less favourable outcome than pure cribriform cancers (28). Cribriform breast cancers consist of the luminal type and have better survival rates (27).

Pathological features of invasive lobular carcinomas are small, uniform, epithelial cells with intracytoplasmic lumina that are arranged in a single file, and concentric arrays around ducts forming a targetoid appearance (29). The characteristic discohesive growth pattern of lobular carcinomas is the result of dysregulation of cell-cell adhesion properties, primarily driven by the adhesion molecule, E-cadherin. Several types of lobular carcinoma can be recognised according to their morphologic features. In our study, we did not classify cases of lobular carcinomas into subgroups. Lobular breast cancer is associated with a higher age at diagnosis, higher pT stage, higher percentage of multifocal, multicentric, and bilateral cases, lower histological grade, and higher rate of hormone receptor positivity (<95% of cases in recent series) (30). Although the features of our cases are similar to those in the literature, there are some cases that were basal and HER2 types with high grades. This was probably due to the subgroups of lobular carcinoma-like pleomorphism, which has more cellular atypia and increased mitotic rate. Lobular tumors have more favourable outcomes than ductal carcinomas during short-term follow-up periods but worse prognoses than ductal carcinomas in the long-term because of the risk of distant metastases after a long period of time.

In our study, it was seen that the patients presented with later stages. Patients in stage III constituted 24.6% of all study patients, which is worrisome. On the other hand, patients in stage II constituted 54.7% of all study patients. The stage distribution of patients with special type breast cancers in our study was similar to the results of our breast cancer stage distribution (31). The delay in the treatment in all kinds of breast cancer in our country presents a great problem and can only be reduced by increased breast cancer awareness, implementation of organized population-based screening programmes, and funding cancer centres (32). Late presentation is not specific to special type tumors but is a national health problem. Our results were in accordance with the data in the literature.

Molecular classification of breast tumors is gaining more importance because chemotherapy, hormone therapy, and surgical treatments are decided according to molecular patterns of the tumors. Generally luminal-type tumors are composed of mucinous, tubular, lobular, and micropapillary tumors. The HER2 type is generally composed of lobular, micropapillary, and apocrine tumors. Basal-like tumor type is generally composed of medullary and metaplastic breast tumors (2). Our results are compatible with those reported in the literature.

All of the cases with micropapillary, cribriform, apocrine, and tubular breast tumors, which are the luminal type, had DCIS lesions in our study. However, only a minority of mucinous and lobular breast tumors were accompanied by DCIS. Several genetic changes were present in DCIS progression. Microenviromental changes are another factor for DCIS progression (33). There is, however, no clear relationship between DCIS and special type breast tumors. The ratio of existence of DCIS in our study was 28%. This ratio was similar with ratios (20%-25%) of DCIS existence in newly diagnosed breast cancer (33).

This study showed the importance of molecular characteristics of different histological breast cancer types. Understanding the underlying molecular features of special types of breast cancer will provide new approaches and new study areas for the treatment modalities. There are several genetic alterations that might help target the treatment (34). With the increase in the understanding of genetic background of the breast cancer in different geographic regions, we can target the new treatment approaches. The molecular types, grades, and stages of special type tumors can change in different regions depending on race, cancer prevention programs, and geographic regions (25). We thought that this study would be the helpful and informative for future studies about special type breast tumors and molecular patterns in this geographic region. Although the distribution of special type breast tumors among molecular types are similar with those reported in the literature, there were exceptions in our cases. These exceptions might have been related to race, late diagnosis, and enviromental factors. Lack of data about personal history, treatment modalities, BRCA gene mutations, and risk factors are the limitation of our study. As the number of cases is limited, multicenter national studies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University Local Ethical Committee (KOU KAEK 2015/261).

Informed Consent: Written informed consent was not recieved due to the retrospective natüre of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.U.Y.; Design - T.U.Y., L.T.; Supervision - C.E., Z.U.; Resources -S.A.T., M.A.B.; Materials - G.P., S.A.T.; Data Collection and/or Processing - T.U.Y., L.T., M.A.B.; Analysis and/or Interpretation - T.U.Y., L.T., C.E.; Literature Search - T.U.Y., M.A.B.; Writing Manuscript - T.U.Y., L.T.; Critical Review - C.E., Z.U.

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