



Special types of breast cancer: Clinical, Histological Features and Survival Outcomes

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ABSTRACT

Objective: In this study, we investigated the clinical characteristics and survival outcomes of patients diagnosed with special types of breast cancer who presented to our clinic.

Methods: The demographic, clinicopathological, and survival characteristics of all rare, histologically special subtype breast cancer patients who applied to Sivas Cumhuriyet University Oncology Center between 2010 and 2020 were retrospectively reviewed.

Results: The records of 1198 patients with invasive breast cancer were examined, and 104 of them (8%) were identified as having other histological special subtypes. Of these, 19 (8%) had apocrine cancer, 19 (8%) had mucinous type, 17 (7%) had invasive cribriform, 15 (6%) had invasive papillary, 11 (4%) had metaplastic type, 9 (4%) had invasive micropapillary, 6 (2%) had neuroendocrine, 3 (1%) had tubular type, 3 (1%) had microinvasive type, and 2 (1%) had undifferentiated carcinoma. The majority of these patients, 102 (98%), were female, with a median age of 52 years (range 26-82). Of the women, 60 (59%) were postmenopausal, and 42 (41%) were premenopausal. The ECOG Performance Score (PS) was 0 in 79 (76%) patients, 1 in 17 (16%) patients, and 2 in 8 (8%) patients. Upon evaluation, 50 patients (48%) had comorbid conditions, and 26 patients (25%) had a family history of breast cancer. At diagnosis, 25 patients (24%) were stage I, 50 (48%) were stage II, 26 (25%) were stage III, and 3 (3%) were stage IV. Histopathologically, 75 patients (72%) were estrogen receptor (ER)-positive, 69 (66%) were progesterone receptor (PR)-positive, and 26 (25%) were HER2-positive. An intraductal component was detected in 54 (60%) patients, and multicentricity was observed in 15 (16%) patients. A modified radical mastectomy was performed on 56 (54%) patients, while breast-conserving surgery was performed on 45 (43%) patients. Adjuvant chemotherapy was administered to 76 (73%) patients, hormonal therapy to 73 (70%), and radiotherapy to 72 (68%). The median follow-up period was 54 months (range 1-201). During follow-up, metastasis was detected in 13 patients (13%), and recurrence was detected in 7 patients (7%). The 5-year and 10-year overall survival rates were 86% and 77%, respectively, while the 5-year and 10-year event-free survival rates were 79% and 70%, respectively.

Conclusion: In our study, the majority of patients with special type breast carcinoma were non-metastatic, and histopathologically, they were hormone receptor-positive with low grade. There was no statistically significant difference in 5-year and 10-year overall survival or event-free survival among the special types.

Keywords: Breast Cancer, Special types of breast cancer, overall survival, event-free survival

Özel Tip Meme Karsinomları: Klinik, Histolojik Özellikleri ve Sağkalım Sonuçları

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ÖZET

Amaç: Bu çalışmada kliniğimize başvuran özel tip meme kanseri tanımlı hastaların klinik özelliklerini ve sağkalım sonuçlarını araştırdık.

Yöntem: Sivas Cumhuriyet Üniversitesi Onkoloji Merkezi'ne 2010-2020 yılları arasında başvuran meme kanserli tüm nadir, histolojik olarak özel alt tip hastalarının demografik, klinikopatolojik ve sağkalım özellikleri retrospektif olarak incelenmiştir.

Bulgular: Çalışmada 1198 invaziv meme kanserli hastaların dosyaları incelenmiş ve bunlardan 104'ünün (8%) diğer histolojik özel alt tipinde olduğu tespit edilmiştir. Apokrin kanser 19 (8%), musinöz tip 19 (8%), invaziv kribriform 17 (7%), invaziv papiller 15 (6%), metaplastik tip 11 (4%), invaziv mikropapiller 9 (4%), nöroendokrin 6 (2%), tubuler tip 3 (1%), mikroinvaziv 3 (1%), undifferansiyel 2 (1%) hastada saptanmıştır. Bu hastaların büyük bir kısmı 102 (98%) si kadın olup median yaşı 52 (26-82) bulunmuştur. Kadınların 60 (%59)'u postmenopozal, 42 (41%)'isi de premenopozaldır. 79 (76%) hastanın ECOG Performans skoru (PS) 0, 17 (16%)'sinin ECOG PS 1, 8 (8%)'inin ECOG PS 2 olarak izlenmiştir. Hastalar sorgulandığında 50'sinde (48%) komorbid hastalıklar olduğu, 26'sinde (25%) ailede meme kanseri öyküsü olduğu görülmüştür. Tanıda 25 (24%) hastanın evre I, 50 (48%) hastanın evre II ve 26 (25%) hastanın evre III, 3 (3%) hastanın evre IV olduğu tespit edilmiştir. Histopatolojik değerlendirmelere göre hastaların 75'inde (72%) estrogen reseptörü (ER) pozitif, 69'ünde (66%) progesterone reseptörü (PR) pozitif, 26'sında (25%) HER2-pozitif olarak bulunmuştur. İntraduktal component 54 (60%) hastada tespit edilmiştir. Multisentrisite 15 (16%) hastada izlenmiştir. 56 (54%) hastaya modifiye radikal mastektomi, 45 (43%) hastaya meme koruyucu cerrahi uygulanmıştır. 76 (73%) hastaya adjuvant kemoterapi, 73 (70%) hastaya hormonoterapi ve 72 (68%) hastaya radyoterapi verilmiştir. Medyan takip 54 (1-201) ay olup takipte 13 (13%) hastada metastaz, 7 (7%) hastada nüks tespit edilmiş. Hastaların 5 ve 10 yıllık overall survival sırasıyla 86% ve 77% olup, 5 ve 10 yıllık event-free survival sırasıyla %79 ve %70 olarak bulunmuştur.

Sonuç: Çalışmamızda özel tip meme karsinomu hastaların tamamına yakını nonmetastatik olup histopatolojik olarak hormon reseptörü pozitif ve düşük gradelidir. Özel tipler arasında, 5 ve 10 yıllık overall survival/ event-free survival istatistiki olarak anlamlı bulunmamıştır.

Anahtar Kelimeler: meme kanseri, özel tip, genel sağkalım, olaysız sağkalım

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Introduction

Breast cancer is a heterogeneous disease and according to the WHO classification, breast cancer can be categorized into 21 different histological types based on their varying morphological and growth features.¹ Invasive ductal carcinoma is the most common histological type. Among the histological special subtypes of breast carcinoma are tubular carcinoma (2%), medullary carcinoma (1%), papillary carcinoma, metaplastic carcinoma (less than 1%), and other epithelial tumors such as squamous cell carcinoma, as well as mesenchymal and stromal tumors/fibroepithelial tumors. Major studies that have defined molecular subtypes have almost exclusively focused on invasive ductal breast cancers, without including rare histological subtypes.⁴ Although clinical, pathological, and epidemiological differences between ductal and lobular carcinomas have been examined in numerous studies, information regarding rarer histological subtypes such as mucinous, tubular, medullary, and papillary carcinomas is still not well understood.²⁻⁵ Our understanding of these subtypes primarily relies on various case reports and studies based on small clinical series.^{2,3} Histopathological classification has prognostic significance. For instance, tubular carcinoma is associated with a good prognosis, while metaplastic cancer is linked to a poor prognosis.^{2,3} In this study, we examined the clinical, histopathological, and survival characteristics of patients diagnosed with special types of breast cancer who presented to our results.

Materials and Methods

This study was conducted with 104 patients diagnosed with special types of breast cancer among 1166 patients treated and followed up between 2010 and 2020 at Sivas Cumhuriyet University department of radiation oncology. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the the local ethics committee of Sivas Cumhuriyet University.

Patient Selection

In this study for patient selection, female patients >18 aged, diagnosed with special types of breast cancer at all stages were included. Clinicopathological data were obtained from the patients' files and medical records. Information regarding age at diagnosis, comorbidities, family history, menopausal status, follow-up, treatments, recurrence site and vital status were gathered from the files and medical records. Patients who were amenorrheic for more than 6 months before the diagnosis of breast cancer, those receiving hormone replacement therapy, or those who were at least 50 years old and whose menopausal status was not indicated in the medical records were considered postmenopausal.

At the time of diagnosis, all patients were staged according to the 8th Edition of the American Joint Committee on Cancer staging manual. The performance status of the patients was assessed according to Eastern Cooperative Oncology Group (ECOG) scoring system.

HER2 testing was performed using immunohistochemistry (IHC) or in situ hybridization (ISH).⁶ Hormone receptor for ER and PR was used the method specified in the guidelines.⁷ The subgroup classifications of patients as luminal type A and B,

HER2 overexpression type, and triple-negative were according to the St. Gallen International Expert Consensus.⁸

The overall survival (OS) was defined as the time from diagnosis to the last follow-up or death. The time from diagnosis to recurrence/distant metastasis, death or last follow-up in those without recurrence/metastasis was defined as event-free survival (EFS).

Statistics

Statistical analyses of all data were conducted using "IBM SPSS Statistics for Windows, (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA) Version 23.0" Student's T test (normal distribution) or Mann-Whitney U test (abnormal distribution) were used to compare the groups for non-categorical variables. Chi-square test was used to compare categorical variables. Kaplan-Meier test was used to determine survival times. A p-value < 0.05 was considered statistically significant.

Results

In this study, 1198 breast cancer patients were reviewed, with 5.5% (n=104) identified as having special histological subtypes. The median age of these patients was 52 years (range 26-82). At the time of diagnosis, 60% were postmenopausal. Comorbidities were present in 50% of the patients and 25% had a family history of breast cancer. At diagnosis, 48% of the patients were in stage II. The demographic and clinical characteristics of the patients were presented on the table 1.

ER positivity was present in 72% of the patients, 66% were progesterone receptor (PR)-positive, and 25% were HER2-positive. The median Ki67 index was 20%. The molecular subtypes were distributed as follows: 31% were luminal A, 26% were luminal B HER2-negative, 17% were luminal B HER2-positive, 8% were HER2-positive, and 18% were triple-negative. An intraductal component was observed in 60% of patients, and in 65% of these patients, the intraductal component accounted for less than 25% of the tumor. Multicentricity was detected in 16% of the patients. Table 2 was summarized the histopathological characteristics of the patients.

Seven different histological types of breast tumors were evaluated. The demographic and clinical characteristics of the more common (>5) breast cancer subtypes were presented in table 1. Treatments were administered according to the standards of our center. Adjuvant chemotherapy (CT) and radiotherapy (RT) were applied based on risk factors (age, tumor size, regional lymph node involvement, etc.). Accordingly, 54% of the patients underwent modified radical mastectomy (MRM) and 69% underwent axillary dissection. The majority of patients received adjuvant therapies (chemotherapy, hormonotherapy and radiotherapy were administered to 73%, 70% and 68% of patients, respectively). Among early-stage patients, local recurrence was observed in 7% during follow-up, while the metastasis rate was 13%, with bone being the most common site of metastasis. The treatments administered to the patients and the patterns of recurrence and metastasis were presented in table 3. The median follow-up period was 54 months (range 1-201). Survival outcomes of the patients were presented in tables 4 and 5. Accordingly, the 5-year OS and EFS were 86% and 79%, respectively, while the 10-year OS and EFS were 77% and 70%, respectively.

Table 1. Demographic and clinic characteristics of patients

	Number of patients n=104	%
ECOG Performance status		
0	79	76
1	17	16
2	8	8
Menopausal status		
Premenopausal	42	41
Postmenopausal	60	59
Comorbidity	50	48
Diabetes mellitus	20	19
Hypertension	36	35
Heart disease	11	11
Family history+	26	25
T stage		
T1	34	33
T2	45	43
T3	18	17
T4	4	4
Tx	3	3
N stage		
N0	58	56
N1	22	21
N2	16	15
N3	8	8
Stage		
I	25	24
II	50	48
III	26	25
IV	3	3

ECOG Performance status: Eastern Cooperative Oncology Group Performance status

Table 2. Pathological characteristics of patients

	Number of patients n=104	%
ER Status		
Negative	29	28
Positive	75	72
PR Status		
Negative	35	34
Positive	69	66
Ki67 (Median, %)	20	0-95
HER2 Status		
Negative	78	75
Positive	26	25
Histological Subtypes		
Luminal A	32	31
Luminal B (HER2-negative)	27	26
Luminal B (HER2-positive)	18	17
HER2-positive	8	8
Triple-negative	19	18
Grade		
1	44	42
2	37	36
3	23	22
Lymphovascular invasion (n=91)		
Negative	60	66
Positive	31	34
Perineural invasion (n=88)		
Negative	72	82
Positive	16	18
Intraductal component (n=90)		
No	36	33
Yes	54	67
Intraductal component ratio (n=54)		
<%25	35	65
≥%25	19	35
Multifocality (n=96)		
No	81	84
Yes	15	16
Tumor necrosis (n=82)		
No	50	85
Yes	32	15
Extracapsular invasion (n=100)		
No	76	76
Yes	24	24

ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

Table 3. Treatments received by patients and recurrence-metastasis patterns

	Number of patients n=104	%
Surgery		
No	3	3
MRM	56	54
BCS	45	43
Axillary Surgery		
No	3	3
SLNB	29	28
AD	72	69
Adjuvant Treatments		
Chemotherapy	76	73
Hormonoterapi	73	70
Radiotherapy	72	68
Local relapse	7	7
Metastasis	13	13
Metastasis sites		
Bone	11/13	11
Brain	5/13	5
Lung	3/3	3
Liver	3/3	3

MRM: Modified Radical Mastectomy, BCS: Breast Conserving Surgery, SLNB: Sentinel Lymph Node Biopsy, AD: Axillary Dissection

Table 4. Overall Survival outcome of patients

Number of patients n=104	5 yıllık Overall survival %	10 yıllık Overall survival %	p value
Apocrine	74	65	0.714
Neuroendocrine	80	60	
Mucinous	88	81	
Metaplastic	82	72	
Invasive	88	76	
Cribriform			
Invasive	78	78	
Micropapillary			
Invasive Papillary	78	62	

Table 5. Event-free survival outcome of patients

Number of patients n=104	5-year Event-free survival %	10-year Event-free survival %	p value
Apocrine	68	52	0.490
Neuroendocrine	63	42	
Mucinous	81	81	
Metaplastic	72	72	
Invasive	88	66	
Cribriform			
Invasive	56	56	
Micropapillary			
Invasive Papillary	80	64	

Discussion

Special types of breast cancers are rare and due to their infrequency, comprehensive clinical evaluations have not been conducted, leading to a limited understanding of their distinct clinical features. Most of the available data on treatment strategies come from small series and case reports, leaving clear recommendations for clinical management still lacking. As a result, current international guidelines generally recommend the use of chemotherapy regimens typically applied for invasive ductal carcinoma, where indicated, in patients with special types of breast cancer. However, this recommendation reflects the absence of robust prognostic data. This study has identified the characteristics of special type breast tumors. The correlation between histological type and prognosis is well established. The good prognosis group; cribriform, tubular, mucinous and the intermediate prognosis group; invasive micropapillary and medullary carcinoma, the poor prognosis group; mixed ductal and solid lobular, metaplastic and high-grade neuroendocrine carcinoma.¹ In this study, the histological types with the best prognosis were mucinous and tubular carcinomas, while the worst OS was observed in the apocrine and neuroendocrine carcinoma groups.

Apocrine carcinoma is a neoplasm predominantly composed of apocrine-type epithelium.⁹ In a published retrospective analysis involving more than 6,800 invasive

ductal carcinoma cases and 72 cases of apocrine carcinoma. Apocrine carcinoma was independently associated with a poorer disease-free survival (DFS), whereas invasive ductal carcinoma breast cancer showed similar outcomes.¹⁰ In our study, apocrine carcinoma accounted for 0.15% of breast cancer cases. The 5-year OS and EFS were 74%, 68%.

Mucinous carcinomas represent 1-4% of all breast cancers and they are typically diagnosed at older ages.¹¹ In our study, this carcinoma subtype comprised 0.15% of breast cancer cases. Mucinous carcinomas are generally luminal type, low-grade, and associated with a favorable prognosis. Previous studies have reported a 5-year OS rate of 94% and a 10-year survival rate of 89%.¹¹ In our study, the 5-year OS was 88%, and the 10-year OS was 81%, consistent with prior findings.

Invasive micropapillary carcinoma is a rare breast tumor characterized by clusters of cells without fibrovascular cores within stromal spaces and is associated with a poor prognosis. Lymphovascular invasion is commonly observed.¹²⁻¹³ In our cohort, 9 cases were identified, with a 10-year OS of 78%. In the literature, a study with 98 cases reported a 10-year OS of 48%.¹³

Metaplastic carcinomas are tumors that include sarcoma-like spindle cell areas, squamous differentiation, and chondroid or osseous differentiation along with adenocarcinoma.¹⁴⁻¹⁷ These are typically high-grade tumors, with a prognosis worse than triple-negative invasive ductal carcinoma.¹⁵ In our study, the 5-year OS was 82%, and the 10-year OS was 72%. The incidence of metaplastic breast

carcinoma ranges from 0.2-0.6%, and in our study, this rate was 0.09%.

Neuroendocrine carcinomas of the breast are defined by the presence of neuroendocrine features with widespread expression of neuroendocrine markers. Their prevalence can reach up to 0.5% of breast cancers.¹⁸ In our study, the incidence was 0.05%. Neuroendocrine tumors typically have a favorable prognosis; however, the high-grade small cell variant is associated with a poor prognosis. In our study, the 5-year OS was 80%, and the 10-year OS was 60%, with clinical-pathological features aligned with literature data.

Invasive cribriform carcinomas (ICC) represent 0.3-0.8% of breast cancers.²⁰ In our study, ICC comprised approximately 0.14% of cases, with a 5-year OS of 88% and a 10-year OS of 76%. These tumors are typically ER+, low-grade, and exhibit low proliferation, reflecting a favorable prognosis.

Overall, in our study, the majority of patients presented at stage 2 and stage 3. Early-stage patients constituted 72% of the entire cohort.

Limitations

Retrospective analysis, small groups of patients, lack of more detailed new molecular and genetic testing were limitations of this study.

Conclusion

The clinical management of special histological types of breast cancer presents a genuine challenge, and clear guidelines are still lacking. These tumors represent a heterogeneous group with rare, diverse behaviors and prognoses, making prospective studies impractical. It remains debated whether patients with special type breast carcinomas have a better prognosis. Clinical experience is important, as each case contributes to understanding the characteristics of these tumors and helps in making the most appropriate treatment decisions. Our results were generally consistent with data from other studies, except for some cases. These discrepancies may be related to variations in pathological assessment and environmental factors.

Declarations

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Author's contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by EDA ERDİŐ. The first draft of the manuscript was written by EDA ERDİŐ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: The present study was performed in line with the principles of the Declaration of Helsinki.

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