Original Research Article

COMPARISON OF RARE TYPES BREAST CANCER

ABSTRACT

Aims: Mucinous, medullary and papillary carcinomas are rarely encountered types of breast cancer. This study is directed towards comparing clinical and prognostic features of and treatment alternatives for rare breast carcinomas.

Study design: Thirty-four patients operated for rare breast cancer between January 2011 and December 2020 were included into 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 lymph nodes removed through axillary dissections and the number of 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 hormone receptor status of these tumors. Long-term survival differed between rare breast tumors. In view of unique clinical pictures of the tumors, patients should be evaluated individually and the evaluation should be associated with evidence-based principles available for more common breast carcinomas.

Key Words: 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 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 and medical 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 carcinomas not needing aggressive treatment, unresponsive to treatment and requiring aggressive treatment (3).

There has been a widespread insight into 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 (9). There are 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 pattern (8).

There have been many studies on the effects of molecular subtypes of 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 (2,3,11,12,13,14).

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 (10,15,16). Despite increased evidence, biological behavior patterns of rarely encountered histological subtypes of breast cancer are still unclear.

The aim of the present study was to compare clinical and prognostic features and treatment modalities of rare breast carcinomas in the patients treated and followed in our clinic.

2. PATİENTS AND METHODS

2.1 Patient selection

After obtaining ethical approval from Adana City Education and Research Hospital Ethical Board (IRB No. 10.03.2021/76/1327), 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 pathological examination reports.

The patients diagnosed as invasive ductal carcinoma and invasive lobular carcinoma on pathological examination 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 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 patient and hospital records. The latest data were gathered through death records or phone calls depending of survival status of patients. The patients about whom sufficient clinical data were not available in 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. 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 lymph nodes removed through axillary dissection and the number of 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 Group1, 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 tumor grade was higher in Group 1. In fact, 70% of the patients in Group 1 had grade 3 tumors (p:0.023). 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 Group1, 100% of Group 2 and 100% of Group 3; p<0,001). Group 2 had a lower survival at the time of study (93% of Group 1, 60% of Group 2 and 100% of Group 3; p:0,024). Data collected during oncological follow-up 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 5 and Figure 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.

Table 1. Demographic and Surgical and Pathological Variables

	Medullary n(%)	Mucinous n(%)	Papillary n(%)	Total n(%)	p
Gender					
Female	15 (100)	10 (100)	8 (88,9)	33 (97,1)	0,239
Male	0 (0)	0 (0)	1 (11,1)	1 (2,9)	
Laterality					
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)	
Age (years) Median (Min-Max)	58 (32-74)	58 (38-93)	65 (45-76)	59 (32-93)	0,350
Neoadjuvant treatment					
Yes	4 (26,7)	3 (30)	0 (0)	7 (20,6)	0,200
No	11 (73,3)	7 (70)	9 (100)	27 (79,4)	
Surgery					
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)	
SLNB	2 (13,3)	4 (40)	3 (33,3)	9 (26,5)	0,288
The number of lymph nodes removed through axillary dissection	20 (10-44)	16 (10-32)	14,5 (11-20)	18 (10-44)	0,093
The number of positive lymph nodes	0 (0-3)	0 (0-2)	0,5 (0-4)	0 (0-4)	0,710
Tumor size (mm)	30 (7-100)	42,5 (12-65)	30 (8-55)	32,5 (7-100)	0,464
ER					
Positive	5 (33,3)	10 (100)	9 (100)	24 (70,6)	**<0,001**
Negative	10 (66,7)	0 (0)	0 (0)	10 (29,4)	
PR					
Positive	5 (33,3)	10 (100)	7 (77,8)	22 (64,7)	**0,002**
Negative	10 (66,7)	0 (0)	2 (22,2)	12 (35,3)	
HER2					
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)	
DCIS					
Yes	3 (20)	3 (30)	4 (44,4)	10 (29,4)	0,445
No	12 (80)	7 (70)	5 (55,6)	24 (70,6)	
Grade					
1	0 (0)	1 (20)	2 (28,6)	3 (13,6)	**0,023**
2	3 (30)	4 (80)	4 (57,1)	11 (50,0)	
3	7 (70)	0 (0)	1 (14,3)	8 (36,4)	

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-Up

	Medullary n(%)	Mucinous n(%)	Papillary n(%)	Total n(%)	p
Chemotherapy					
Yes	14 (93,3)	3 (30)	8 (88,9)	25 (73,5)	**0,001**
No	1 (6,7)	7 (70)	1 (11,1)	9 (26,5)	
Radiotherapy					
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)	
Hormonotherapy					
Yes	4 (26,7)	10 (100)	9 (100)	23 (67,6)	**<0,001**
No	11 (73,3)	0 (0)	0 (0)	11 (32,4)	
Recurrences					
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)	
Mortality					
Yes	1 (6,7)	4 (40)	0 (0)	5 (14,7)	**0,024**
No	14 (93,3)	6 (60)	9 (100)	29 (85,3)	

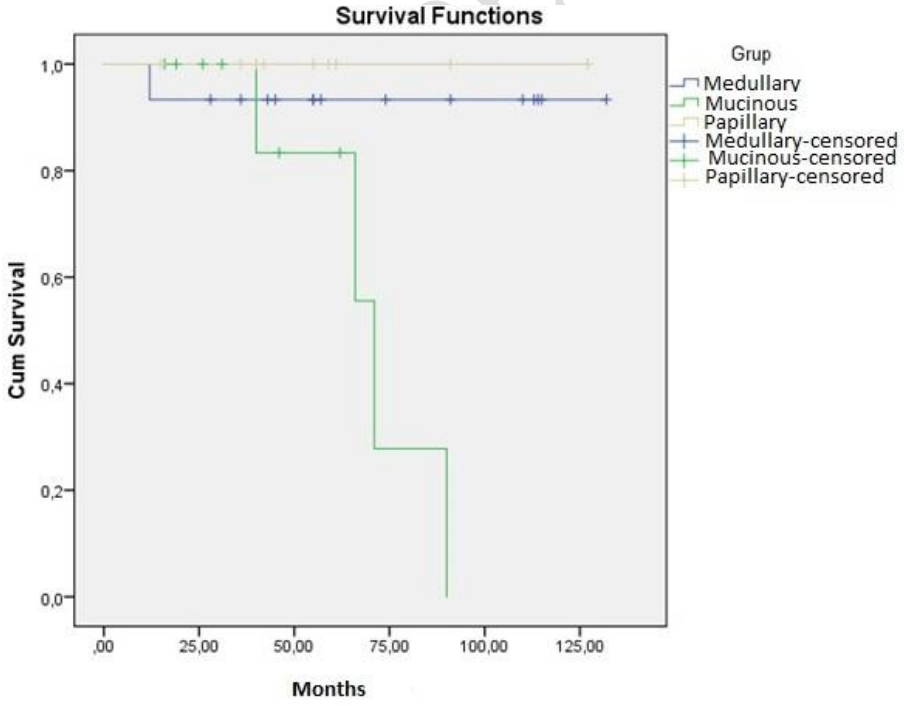

Figure 1. Survival Rates

Table 3: Duration of Survival

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

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. However, 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 invasive breast carcinomas and displaying a favorable prognosis in spite of its aggressive morphological features. 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 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).

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. Findings from Han's study confirmed 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 a 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 hormonotherapy since hormone receptors were negative. As opposed to histopathological features, cases of mucinous breast carcinoma had a lower survival and a higher death rate during follow-up.

The limitations of the present study were its limited number of patients and retrospective nature. However, the results of the study still make a contribution 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 hormone receptor status of these tumors. There were differences in long-term survival between rare breast cancer carcinomas. Time to recurrences was shorter in cases of mucinous breast carcinoma. Large meta-analyses are needed to provide a better insight into differences of biological behavior between rare breast carcinomas.

CONSENT

Written informed consent was obtained from all the patients.

ETHİCAL APPROVAL

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

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REFERENCES

1. Cadoo KA, McArdle O, O'Shea AM, Power CP, Hennessy BT. Management of unusual histological types of breast cancer. Oncologist. 2012;17(9):1135-45. doi: 10.1634/theoncologist.2012-0134

2. Solanki M, Visscher D. Pathology of breast cancer in the last half century. Hum Pathol. 2020;95:137-148. doi: 10.1016/j.humpath.2019.09.007.

3. Tsang JYS, Tse GM. Molecular Classification of Breast Cancer. Adv Anat Pathol. 2020;27(1):27-35. doi: 10.1097/PAP.0000000000000232

4. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2019; 69(1): 7-34. doi: 10.3322/caac.21551

5. Erdogan O, Yuksel U M, Berberoğlu U, Gulben K, Aksel B, Uyar O et al.The Accuracy of Memorial Sloan-Kettering Cancer Center Nomogram in Anatolian Breast Cancer Patients. Acta Oncol Tur. 2016; 49(3): 151-157 | DOI: 10.5505/aot.2016.04127

6. Türkyılmaz M, Hacıkamiloğlu E, Deniz EB, Boztaş G, Dündar S, Ergün AK, et al. Türkiye Kanser İstatistikleri 2015. TC Sağlık Bakanlığı, Halk Sağlığı Genel Müdürlüğü, Ankara 2018.

7. Breast Cancer, Turkey. In: WHO, editor.: GLOBOCAN 2018, International Agency for Research on Cancer; 2018.

8. Tavassoli FA, Devilee P. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon, France: IARC Press Breast Cancer Research 2004;6:133.

9. Yerushalmi R, Hayes MM, Gelmon KA. Breast carcinoma--rare types: review of the literature. Ann Oncol. 2009;20(11):1763-70. doi: 10.1093/annonc/mdp245.

10. Gök M, Topal U, Öz B, Akgün H, Akcan AC, Sözüer EM. Comparison of Clinical Features and Treatment Results of Mix Mucinous Carcinomas and Other Atypical Carcinomas of the Breast. Eur J Breast Health. 2019;1;15(4):222-228. doi: 10.5152/ejbh.2019.5032.

11. Williams LA, Hoadley KA, Nichols HB, Geradts J, Perou CM, Love MI et al. Differences in race, molecular and tumor characteristics among women diagnosed with invasive ductal and lobular breast carcinomas. Cancer Causes Control. 2019;30(1):31-39. doi: 10.1007/s10552-018-1121-1.

12. Gupta I, Sareyeldin RM, Al-Hashimi I, Al-Thawadi HA, Al Farsi H, Vranic S et al. Triple Negative Breast Cancer Profile, from Gene to microRNA, in Relation to Ethnicity. Cancers (Basel). 2019;13;11(3):363. doi: 10.3390/cancers11030363.

13. Kahraman M, Röske A, Laufer T, Fehlmann T, Backes C, Kern F et al. MicroRNA in diagnosis and therapy monitoring of early-stage triple-negative breast cancer. Sci Rep. 2018;2;8(1):11584. doi: 10.1038/s41598-018-29917-2.

14. Lai J, Wang H, Pan Z, Su F. A novel six-microRNA-based model to improve prognosis prediction of breast cancer. Aging (Albany NY). 2019;30;11(2):649-662. doi: 10.18632/aging.101767.

15. Yıldırım N, Aldemir MN, Şimşek M, Bilici M, Tekin SB. Nadir Meme Tümörleri. Bakırköy Tıp Dergisi 2019;15:232-9. DOI: 10.4274/BTDMJB.galenos.2019.20180815080623

16. Poirier É, Desbiens C, Poirier B, Boudreau D, Jacob S, Lemieux J et al. Characteristics and long-term survival of patients diagnosed with pure tubular carcinoma of the breast. J Surg Oncol. 2018;117(6):1137-1143. doi: 10.1002/jso.24944.

17. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol. 1998;11:155–168.

18. Shousha S. Oestrogen receptor status of breast carcinoma: Allred/H score conversion table. Histopathology. 2008;53:346–347. doi: 10.1111/j.1365-2559.2008.03075.x

19. Masood S. Breast cancer subtypes: morphologic and biologic characterization. Womens Health (Lond). 2016;12(1):103-19. doi: 10.2217/whe.15.99..

20. Dumitru A, Procop A, Iliesiu A, Tampa M, Mitrache L, Costache M et al. Mucinous Breast Cancer: a Review Study of 5 Year Experience from a Hospital-Based Series of Cases. Maedica (Bucur). 2015;10(1):14-8. .

21. Zheng YZ, Hu X, Shao ZM. Clinicopathological Characteristics and Survival Outcomes in Invasive Papillary Carcinoma of the Breast: A SEER Population-Based Study. Sci Rep. 2016;7;6:24037. doi: 10.1038/srep24037.

22. Han Y, Wang J, Xu B. Clinicopathological characteristics and prognosis of breast cancer with special histological types: A surveillance, epidemiology, and end results database analysis. Breast. 2020;54:114-120. doi: 10.1016/j.breast.2020.09.006.

23. Vo T, Xing Y, Meric-Bernstam F, Mirza N, Vlastos G, Symmans WF et al. Long-term outcomes in patients with mucinous, medullary, tubular, and invasive ductal carcinomas after lumpectomy. Am J Surg. 2007;194(4):527-31. doi: 10.1016/j.amjsurg.2007.06.012.