ORIGINAL ARTICLE

Comparison of Clinical, Histopathological, and Survival Outcomes of Pure and Mixed Mucinous Breast Carcinoma

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Abstract

Mucinous breast carcinoma (MBC) is a particular type of breast cancer involving the presence of extracellular mucin. MBC accounts for approximately 4% of invasive breast cancers. MBC is divided into two as pure mucinous breast carcinoma (PMBC) and mixed mucinous breast carcinoma (MMBC) according to cell cellularity ratio. We aimed to investigate the difference between MBC subtypes in terms of clinical and survival. The data of 33 patients who were operated on for MBC between January 2010 and January 2021 in our clinic were analyzed retrospectively. Demographic data, hospital admission complaints, radiological diagnostic methods, surgical technique, histopathological and immunohistochemical examination, and survival time of the patients included in the study were examined. The patients were divided into two groups, PMBC and MMBC, and compared. During the study, MBC was detected in 33 (2.16%) of 1522 patients operated on with breast cancer diagnosis in our clinic. Of the MBC patients, 23 (69.7%) were PMBC and 10 (30.3%) were MMBC. PMBC and MMBC patients were compared in clinical, histopathological, and survival. In the PMBC group, statistically significant tumor size was larger, and survival time was longer in pathological and radiological terms. In addition, axillary dissection rate and N stage were more advanced in the MMBC group. It is essential to distinguish subgroups as MMBC and PMBC according to the amount of extracellular mucin of MBC. Although PMBC is detected in larger sizes at the time of diagnosis than MMBC, MMBC has more axillary metastases and worse survival because it contains invasive components.

Keywords Breast neoplasms · Survival · Mucinous breast carcinoma

Introduction

Mucinous breast carcinoma (MBC) constitutes approximately 4% (1–6%) of invasive breast cancers [1–3]. It is common in postmenopausal women [4]. On physical examination, MBC is a gelatinous lesion with regular borders and an easily recognizable elastic mass. Tumor size is between 1 and 20 cm (mean = 3 cm). MBC has better survival than other breast carcinoma types since its 10-year survival is 90%.

Histopathological examination reveals superficial solid tumor islets within mucin pools. MBC can be divided into two groups according to cell cellularity ratio as pure mucinous breast carcinoma (PMBC) and mixed mucinous breast carcinoma (MMBC) [5].

While PMBC consists of tumor tissue with extracellular mucin production in more than 90% of the tumor, MMBC infiltrates ductal epithelial components without mucin [2]. Although there are case series in the literature showing that PMBC has a better prognosis and survival than MMBC, the limits of MBC subtypes are still being investigated [2, 6].

This study aimed to compare the MBC subtypes PMBC and MMBC in terms of clinical, radiological, histopathological, and survival and investigate their differences.

Patients and Methods

The data of patients with histopathological diagnosis of mucinous breast carcinoma who underwent surgery for breast cancer in Mersin University Faculty of Medicine, Department of General Surgery between January 2010 and January 2021 were retrospectively analyzed. Thirty-three

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(33) patients (2.16%) were included in the study. Two patients diagnosed with mucinous breast carcinoma due to a biopsy from the breast mass but who did not undergo surgery in our clinic were excluded from the study.

Data Collection

Demographic characteristics of the patients (age, gender), menstrual period, complaints on admission, radiological imaging methods and findings, location of the mass in the breast (right, left), biopsy performed for the mass (core biopsy), the surgical technique (lumpectomy and mastectomy), histopathological data, follow-up, and survival time were recorded. In addition, the data of mammography, breast ultrasonography (USG), and magnetic resonance imaging (MRI) were recorded. In addition, the size of the mass (T stage), the total number of removed and metastatic lymph nodes (N stage), and immunohistochemical data were recorded from the histopathology reports. American Joint Committee on Cancer staging manual used MBC staging [7]. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistical package program were used.

Pure/Mixed Mucinous Carcinoma

On histopathological examination of MBC, there are small cell islands and glandular structures composed of uniform cells floating in large extracellular mucin pools. If the mucin content is more than 90% of the mucin/colloid structure, it is grouped as pure mucinous, and if it is less than 90%, it is grouped as mixed mucinous carcinoma [8]. Therefore, the patients included in the study were divided into two groups as pure and mixed mucinous breast carcinoma according to the postoperative histopathological examination and were compared with each other.

Immunohistochemical Examination

During the histopathological examination, hormone receptors (HR), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 were evaluated by immunohistochemistry (IHC). In the evaluation of ER and PR, those with ≥ 10 (fmol/mg cytosol protein) were grouped as positive and those with < 10 as negative [9]. When HER2 was evaluated with the IHC method, it was determined that if 3(+) HER2 was present in the tumor cell, 1(+) tumor cell did not have HER2, and if 2(+) was found, the presence of HER2 was evaluated by fluorescent in situ hybridization (FISH) method [10]. According to IHC and FISH results, patients were grouped as HER2 negative and positive. In our study, the cut-off limit for Ki67 grouping was 20%. Therefore, patients were divided into Ki67 < 20% low and ≥ 20% high group.

Results

During the study, MBC was detected in 33 (2.16%) patients operated on with breast cancer diagnosis in our clinic. Of the patients with mucinous breast carcinoma, 23 (69.7%) were PMBC and 10 (30.3%) were MMBC.

All of the patients were women. While the mean age was 41.7 (SD 11.1) in the PMBC group 47.3 (SD 11.9) in the MMBC group, there was no significant difference between the groups regarding mean age ($p = 0.21$). When the patients were evaluated according to the menopausal period, 15 (65.2%) of the PMBC patients were premenopausal, 8 (34.8%) were in the postmenopausal period, while 4 (40%) were premenopausal and 6 (60%) were postmenopausal in the MMBC group. There was no significant difference between the groups regarding the menopausal period ($p = 0.18$) (Table 1).

While 26 (78.8%) of the patients with MBC had complaints about a mass in the breast, the mass was detected incidentally in 7 (21.2%) of them. The most common complaint of symptomatic patients was a painless palpable mass (61.5%), followed by nipple retraction (15.4%), skin retraction (15.4%), and nipple discharge (7.7%). There was no significant difference between the groups in terms of the presence of the symptom of a breast mass ($p = 0.16$) (Table 2).

Mammography (61%), breast USG (100%), and MRI (48.5%) were used as radiological imaging modalities. According to the location of the mass, it was located in the right breast in 56.5% of the patients in the PMBC group, and in the left breast in 43.5% of the patients, while it was in the right breast in 60% and the left breast in 40% in the MMBC group. There was no difference between the groups according to the mass's lateralization (right/left) ($p = 0.85$). None of the patients had bilateral breast masses.

All patients had a preoperative biopsy with a core biopsy. According to the PMBC group, in the biopsy results, 8 (34.8) patients were diagnosed with PMBC, while 15 (65.2) patients could not be differentiated into subgroups. According to the biopsy results in the MMBC group, 7 (70%) patients could be diagnosed with MMBC in the preoperative period. While lumpectomy was applied to 16 (69.6%) patients in the PMBC group and 5 (50%) patients in the MMBC group, mastectomy was applied to 7 (30.4%) patients in the PMBC group and 5 (50%) patients in the MMBC group. There was no significant difference between the groups regarding surgical technique preference ($p = 0.28$) (Table 1).

Sentinel lymph node biopsy (SLNB) was applied to all patients for axillary lymph node staging. Axillary

Table 1 Comparison of pure and mixed mucinous carcinoma groups with demographic and clinicopathological data

	All patients ($n=33$) $x \pm SD$	PMBC ($n=23$) $x \pm SD$	MMBC ($n=10$) $x \pm SD$	p value
Age	43.4 ± 11.5	41.7 ± 11.1	47.3 ± 11.9	0.21*
Tumor size				
Radiological size (cm)	2.92 ± 1.04	3.16 ± 0.99	2.37 ± 0.97	0.04*
Pathological size (cm)	2.81 ± 1.19	3.11 ± 1.08	2.11 ± 0.93	0.02*
Total removed lymph node Median (min–max)	14.5 ± 3.29 14 (11–21)	12.7 ± 1.5 13 (10–14)	15.6 ± 3.7 16 (11–21)	0.25*
Metastatic lymph node Median (min–max)	1.9 ± 1.8 1 (1–6)	$1 \pm -$ 1 (1–1)	2.4 ± 2.1 3 (1–6)	0.23*
Follow-up time (months)				0.45*
Median (min–max)	63 (13–109)	61 (13–109)	69 (39–103)	
	n (%)	n (%)	n (%)	
Menopause				
Premenopausal	19 (57.6)	15 (65.2)	4 (40)	0.18**
Postmenopausal	14 (42.4)	8 (34.8)	6 (60)	
Lateralization				
Right	19 (57.6)	13 (56.5)	6 (60)	0.85**
Left	14 (42.4)	10 (43.5)	4 (60)	
Number of mass				
One (1)	29 (87.9)	21 (91.3)	8 (80)	0.57**
Two or more (≥ 2)	4 (12.1)	2 (8.7)	2 (20)	
Preoperative biopsy				
Mucinous	33 (100)	23 (100)	10 (100)	
Pure mucinous	8 (24.2)	8 (34.8)	–	**< 0.01**
Mixed mucinous	7 (21.2)	–	7 (70)	
Indiscriminate	18 (54.5)	15 (65.2)	3 (30)	
Surgical technique				
Lumpectomy	21 (63.6)	16 (69.6)	5 (50)	0.28**
Mastectomy	12 (36.4)	7 (30.4)	5 (50)	
SLNB	33 (100)	23 (100)	10 (100)	–
Axillary dissection				
Yes	8 (24.2)	3 (13)	5 (50)	**0.02**
No	25 (75.8)	20 (87)	5 (50)	
Five-year survival	29 (87.9)	21 (91.3)	8 (80)	0.57**

*Student t test; **chi-square ($p < 0.05$); Statistically significant p values are indicated in bold

Table 2 Symptoms of patients at admission to hospital

	All patients ($n=33$) n (%)	PMBC ($n=23$) n (%)	MMBC ($n=10$) n (%)
Symptomatic	26 (78.8)	20 (87)	6 (60)
Painless mass	16 (61.5)	15 (75)	1 (17)
Nipple retraction	4 (15.4)	2 (10)	2 (33)
Skin retraction	4 (15.4)	3 (15)	1 (17)
Nipple discharge	2 (7.7)	–	2 (33)
Asymptomatic (incidental)	7 (21.2)	3 (13)	4 (40)

dissection was performed in patients with carcinoma metastasis as a result of SLNB. Axillary lymph node dissection was performed on 3 (13%) patients in the PMBC group and 5 (50%) patients in the MMBC group. It was determined that axillary lymph node metastasis was more common in the MMBC group than in the PMBC group, and there was a significant difference ($p = 0.02$). The median value of the total number of lymph nodes removed by axillary dissection was 13 (10–14) in the PMBC group and 16 (11–21) in the MMBC group. The median value of the number of metastatic lymph nodes was 1 (1), while 3 (1–6) were in the MMBC group. There was no significant difference between the groups in terms of the total number

of lymph nodes removed and the number of metastatic lymph nodes ($p = 0.25$, $p = 0.33$, respectively) (Table 1).

Tumor size was evaluated with radiological imaging methods in the preoperative period and determined after histopathological examination in the postoperative period. According to the results of radiological imaging methods, the mean tumor size was 3.16 (SD 0.99) cm in the PMBC group, while it was 2.37 (SD 0.97) cm in the MMBC group. According to the histopathological examination results, the mean tumor size was 3.11 (SD 1.08 cm) in the PMBC group, while it was 2.11 (SD 0.93) cm in the MMBC group. There was a significant difference between the groups regarding tumor size after radiological and histopathological examination ($p = 0.04$, $p = 0.02$, respectively). The mean tumor size was lower in the MMBC group than in the PMBC group (Table 1).

During the histopathological examination, tumor size, the number of total and metastatic lymph nodes removed, ER, PR, cErbB2, and Ki67 levels were determined and reported in all patients. When evaluated in terms of T stage, there were 6 (26.1%) patients at T1 stage, 16 (69.6%) patients at T2 stage, and 1 (4.3%) at the T3 stage in the PMBC group. There were 3 (30%) patients at the T1 stage and 7 (70%) patients at the T2 stage in the MMBC group. When evaluated in terms of the N stage, 20 (87%) of the patients in the PMBC group were at n0, and 3 (13%) were at n1. Of the patients in the MMBC group, 4 (40%) were at n0, 5 (50%) at n1, and 1 (10%) at n2. While there was no difference between the groups according to the T stage, there was a significant difference according to the N stage ($p = 0.79$, $p = 0.02$, respectively) (Table 3).

When the HR in mucinous carcinoma cells was evaluated, 82.6% of the patients in the PMBC group were positive for ER, 65% for PR, and 26% for HER2, whereas in the MMBC group, 70% of the patients were positive for ER, 60% for PR, and 20% for HER2. The Ki67 rate was 20% or higher in 56.5% of the patients in the PMBC group and 40% of the patients in the MMBC group. There was no significant difference between the groups in terms of ER, PR, and HER2 receptor distribution and Ki67 level ($p = 0.65$, $p = 0.77$, $p = 0.71$, $p = 0.46$) (Table 3).

The mean follow-up period of the patients in the postoperative period was 61 (13–109) months in the PMBC group and 69 (39–103) months in the MMBC group. None of the patients were lost during the follow-up period. There was no difference between the groups regarding follow-up time ($p = 0.45$) (Table 1). In the 109-month follow-up period, those in the PMBC group were found to have a 94% survival rate until the 41st month and 87% from the 53rd month. In the MMBC group, the probability of survival was 89% at the 43rd month and 74% at the 53rd month. A total of four patients died of breast cancer-related causes. Two died in the PMBC group at the 41st and 53rd months, and the other

Table 3 Comparison of pure and mixed mucinous carcinoma groups with histopathological and immunohistochemical data

	All patients (n = 33)	PMBC (n = 23)	MMBC (n = 10)	p value*
	n (%)	n (%)	n (%)	
T stage				
T1	9 (27.3)	6 (26.1)	3 (30)	
T2	23 (69.7)	16 (69.6)	7 (70)	0.79
T3–4	1 (3)	1 (4.3)	–	
N stage				
N0	24 (72.7)	20 (87)	4 (40)	
N1	8 (24.3)	3 (13)	5 (50)	**0.01**
N2	1 (3)	–	1 (10)	
Estrogen receptor				
≥ 10%	26 (78.8)	19 (82.6)	7 (70)	0.65
< 10%	7 (21.2)	4 (17.4)	3 (30)	
Progesterone receptor				
≥ 10%	21 (63.6)	15 (65)	6 (60)	0.77
< 10%	12 (36.4)	8 (35)	4 (40)	
HER2				
Positive	8 (24.2)	6 (26)	2 (20)	0.71
Negative	25 (75.8)	17 (74)	8 (80)	
Ki67				
< 20%	17 (51.5)	13 (56.5)	4 (40)	0.46
≥ 20%	16 (48.5)	10 (43.5)	6 (60)	

*Chi-square ($p < 0.05$); Statistically significant p values are indicated in bold

Table 4 Survival analysis (when factor [inclusion of pure/mixed mucinous component] has an effect on time to death)

| Group	Mean	95% CI lower	95% CI upper
Pure	101.2	91.15	111.32
Mixed	88.9	71.95	105.9
Overall	98.7	89.42	107.94
Hazard ratio	2.25	0.27	18.76

Kaplan–Meier/log rank

two died at the 43rd and 74th months in the MMBC group. As seen in the hazard ratio value, since the confidence interval includes 1, it was determined that the time to exitus (months) did not differ according to the pathology groups (Kaplan–Meier, log-rank $p = 0.35$) (Table 4; Graph 1).

Discussion

Mucinous carcinomas are a rare and specific malignant tumor that accounts for 1–6% of invasive breast cancers [1, 3]. It is often seen in advanced age. They are smooth, soft, and mobile masses on examination. MBC is divided into

Graph 1 Graph of survival (survival) probability (%) versus time (descending curve) by pure/mixed mucinous component content
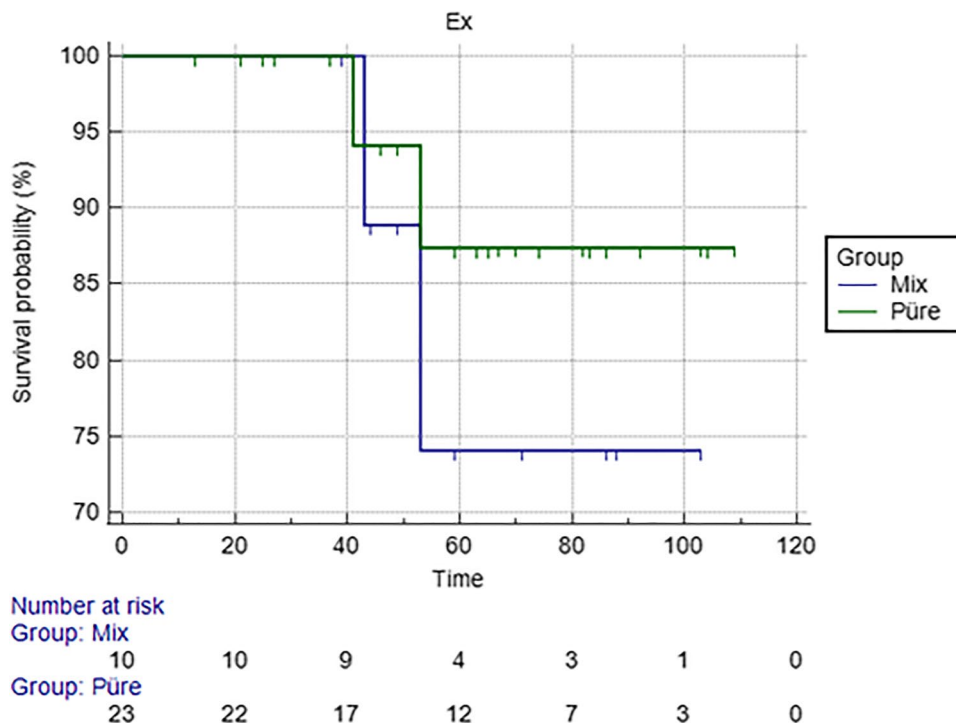
PMBC and MMBC subgroups according to the distribution of mucin-producing cells [8]. In our study, PMBC and MMBC groups were compared in clinical, histopathological, and survival outcomes.

It has been reported that MBC is more common in women in the postmenopausal period, and PMBC is seen at a younger age than MMBC without making a statistical difference [2]. The incidence of MBC in our study was 2.16% and was consistent with the literature. In our study, the PMBC group (41.7, *SD* 11.1) was younger than the MMBC group (47.3, *SD* 11.9), but there was no statistically significant difference between the groups.

Mucinous carcinoma usually grows slowly and can reach a large size at the time of diagnosis. Often the first symptom of patients with MBC is a palpable mass. Sometimes, it can be detected incidentally. Invasion is rarely seen because of its regular borders and growth by pushing the surrounding tissue. MBC subgroups do not have specific symptoms [11, 12]. The most common symptom in our study was a painless palpable mass. There was no difference between the groups in terms of symptoms.

Among the MBC radiological imaging methods, mammography, USG, and breast MRI are used. Radiological imaging methods can show the pure and mixed separation of MBC at different rates. Microlobule borders on mammography are associated with high mucin content, while irregular or pointed borders correspond histologically to lower mucin percentages and infiltrating margins [13]. On USG, MBC is isoechoic or hypoechoic. Homogeneity in USG is associated

with PMBC type and thus a better prognosis. While most PMBCs are isoechogenic to subcutaneous fat echo, MMBC is hypoechogenic [13, 14]. On breast MRI, PMBC contains a limited mass with extremely high signal intensity on the T2 sequence and benign-appearing kinetics with persistent augmentation, whereas MMBC may have more questionable imaging features [15, 16].

When evaluated according to tumor size and TNM stage, there are differences between MBC subgroups. In the study by Chaudhry et al., tumor size was more significant in the PMBC group than in the MMBC group. It was stated that mammography, USG, and breast MRI evaluated tumor size [17]. In our study, the radiology-pathological correlation was found in the measurement of tumor size. In comparing tumor size between the groups, the tumor in the PMBC group was found to be statistically significantly more significant than the MMBC group, both radiologically and pathologically ($p < 0.05$).

When the groups were evaluated according to the TNM staging system, the T stage was more advanced in the PMBC group without creating a statistically significant difference, while the N stage was found to be more advanced in the MMBC group with a statistically significant difference. This was interpreted as the tumor size was primarily due to the high mucin content of PMBC, and MMBC caused more lymph node involvement because it contains more invasive tumor components.

While the biopsy is highly effective for the preoperative diagnosis of MBC, the effectiveness of the biopsy may be

limited in the differentiation of subgroups. In the study of Cyrta et al., a preoperative diagnosis of MMBC with biopsy was detected at 41%, whereas a PMBC diagnosis could not be made. The cytopathological identification of biopsy PMBC patients could not be made adequately [18]. Shield et al. stated that biopsy is sufficient for diagnosing mucinous carcinoma, but it is not possible to differentiate the lesion as PMBC or MMBC [19]. In our study, all patients were diagnosed with MBC by preoperative biopsy. With a biopsy, subgroup discrimination could be made at 34.8% in the PMBC group and 70% in the MMBC group. Therefore, a biopsy was thought to be limited in subgroup discrimination in MBC.

Mucinous tumors usually have high HR positivity in IHC evaluation [20]. Although HR positivity is a better prognostic indicator, it is more common in elderly patients. Rande et al. reported that HR positivity was higher in MBC than in invasive breast cancer, but there was no difference in HR positivity between PMBC and MMBC [21]. In the study by Budzik et al., HR positivity was high, and tumor differentiation was low in the PMBC group [22]. Her2 positivity and high Ki67 level are independent predictive values for breast cancer. However, her2 positivity is mainly low, and Ki67 is low in mucinous carcinoma [23, 24]. There was no significant difference between the groups in our study in terms of ER, PR, and HER2 receptor distribution and Ki67 level [25, 26].

MBC axillary lymph node metastasis is predictive for survival and is seen at a lower rate than invasive ductal and lobular carcinomas of the breast [12]. In subgroups of MBC, axillary lymph node metastasis is more common in MMBC than in PMBC. In MMBC, more axillary lymph node metastases occur because of the characteristics of invasive tumor components [3]. Axillary lymph node metastasis is seen in 2–14% of PMBC and 46–64% of MMBC [13]. SLBN was applied to all patients for axillary lymph node metastasis in our study. Due to SLNB positivity, axillary lymph node dissection was performed at 13% in the PMBC group and 50% in the MMBC group. SLNB positivity and the number of metastatic lymph nodes were statistically higher in the MMBC group ($p = 0.02$).

In the literature, it has been found that PMBC has better 5- and 10-year survival rates than MMBC [26, 27]. When evaluated in terms of 5-year survival rate in their study, Zhang et al. found a higher survival rate for MBC than non-mucinous breast cancer and PMBC than MMBC [26]. Although the 5-year survival rate and survival time were longer in PMBC than in MMBC in our study, there was no statistically significant difference between the groups regarding 5-year survival and survival time ($p = 0.56$ and $p = 0.35$, respectively). In the study by Komenaka et al., PMBC tumor size was larger than MMBC, but it was stated that tumor size did not affect axillary lymph node metastasis and survival.

As the reason for this, they stated that the tumor is filled with mucin in PMBC and does not adversely affect metastasis and survival [28].

Conclusion

Mucinous breast carcinoma has better survival than other breast cancers. In addition, pure mucinous breast carcinoma has a better prognosis than mixed mucinous breast carcinoma due to less lymph node involvement and more hormone receptor positivity. However, because mixed mucinous breast carcinoma has invasive components, it is diagnosed in smaller sizes, has a more aggressive course, and worsens survival. For these reasons, it is imperative to distinguish between pure and mixed mucinous breast carcinoma in mucinous breast carcinoma patients.

Declarations

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