

Comparison of Clinical Features and Treatment Results of Mix Mucinous Carcinomas and Other Atypical Carcinomas of the Breast

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ABSTRACT

Objective: There are multiple subtypes of breast cancer with different biological and pathological features and accordingly exhibit different clinical behaviors. The aim of this study was to compare the treatment modalities, clinical features and prognostic characteristics of Mix Mucinous Carcinomas (MMBC) and other rare tumors of the breast.

Materials and Method: A total of 2152 patients who were operated on for breast cancer in our clinic between 2010-2019, with pathological diagnoses of tubular, pure mucinous, mix mucinous or papillary carcinoma were enrolled in the study. Patients were divided into two groups as mix mucinous patients (Group1) and other rare tumors (Group2). The demographic, clinical and prognostic characteristics and treatment approaches were compared between Groups, and additionally between the subtypes of Group 2.

Results: 42 patients participated in our study. Group 1 consisted of 7 patients, and Group2 consisted of 35 patients. The subtypes in Group2 were papillary (n=21), pure mucinous (n=10) and tubular (n=4). Progesterone Receptor Positivity was found to be significantly higher in Group 2 patients than in Group1 patients (p=0.005, p<0.05). Multicentricity rates in the tumors of the patients in Group1 were found to be statistically significantly higher than the patients in Group 2 (p=0.024, p<0.05). In subtype analysis in Group2, there were no statistically significant differences parameters in the subgroups (p>0.05). Mean survival was 19.5+5.6 (8.5-30.5) months in Group 1 and 46.3+5.2 (36.1-56.6) months, in Group2 when evaluated separately (p:0.002).

Conclusion: The prognosis of pure mucinosis (PMBC) and other atypical cancers of the breast compared to the (MMBC) is quite good. Rare pathological types of breast cancer can have favorable outcomes when treated with necessary oncological principles.

Keywords: Breast neoplasms, pure mucinous breast carcinoma, mix mucinous breast carcinoma

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Introduction

Breast cancer accounts for about 23.8% of all cancers seen in women around the world with around 1,380,600 new cases and 458,000 deaths per year. Looking at the statistics of Turkey in 2015, breast cancer is the most common cancer in women and the incidence is 43.8/100,000 (1, 2).

According to the World Health Organization (WHO) classification, breast cancer can be classified into 21 distinct histological types based on cell morphology, growth and architecture patterns (3). Histopathological classification has a prognostic value. The most common histological type is invasive ductal breast (4).

Invasive papillary carcinoma of the breast constitutes approximately 0.5% of all new breast cancer diagnoses and is the most common breast cancer, usually seen in postmenopausal women. Invasive papillary carcinoma (IPC) is defined as having papillary architecture in >90% of the invasive component (5, 6).

Tubular carcinoma is a well-differentiated breast carcinoma and constitutes less than 2% of all breast carcinomas. This tumor is composed of distinct, well-differentiated tubular structures with open lumens that are lined by a single layer of epithelial cells (3, 7).

Mucinous breast carcinoma, also known as colloid or gelatinous carcinoma, is a rare type and constitutes 1-6% of breast carcinomas. In histopathological examination, small cell islands and glandular structures consisting of uniform cells floating in large extracellular mucin lakes are seen. Hormone receptors are usually positive, the human epidermal growth factor (HER-2/neu) is usually negative (8). Mucinous is defined as a tumor with a mucinous component of 50% or more and divided into pure and mixed subgroups according to the amount of cellularity.

Prognosis of pure mucinosis (PMBC) and Mix Mucinous Carcinomas (MMBC) have a significant distinction between tumor behavior and treatment outcomes. PMBC has a favorable prognosis due to slow growth rates, reduced tumor cell load per unit volume and low lymph node metastases rates, whereas MMBC usually has a worse prognosis, similar to invasive ductal carcinomas. Most studies have reported that PMBC has a slower growth rate and a better prognosis with lower frequency of axillary lymph node metastasis than MMBC (9-11). The 10-year survival reported for PMBC is 87-90%, and for MMBC it is 54-66% (8).

The aim of this study was to compare the treatment modalities, clinical features and prognostic characteristics of MMBC and other rare tumors of the breast.

Materials and Method

A total of 2152 patients who were operated on for breast cancer in Erciyes University General Surgery Department between 2010-2019 were enrolled in the study, after the obtainment of the informed and numbered approval from the Erciyes University School of Medicine Ethics Committee. The final pathological diagnoses of the patients were retrospectively reviewed from the pathology records. Forty-two patients with Tubular, Pure Mucinous, Mix Mucinous or Papillary carcinoma were included in the study. Tumor typing was made according to the World Health Organization criteria (3). Patients were divided into two groups as mix mucinous patients (Group 1) and other rare tumors (Group 2). A common database was created by examining patient files and hospital information system and breast council records. Patient data were evaluated retrospectively using this database. Group 1 and Group 2 were compared. Additionally, the subtypes in Group 2 were compared. The compared parameters include the following; demographic characteristics, comorbid diseases, family history of breast cancer, oral contraceptive use, neoadjuvant chemotherapy status, Breast Imaging and Data System (BI-RADS) as the radiological scoring system (12), tumor localization, multicentricity, multifocality, applied surgical procedure, number of axillary pathological lymph nodes, tumor diameter, receptor status, HER2/neu gene over expression status and pathological stage. Breast cancer was staged according to the sixth edition of the American Joint Committee on Cancer Staging Manual (13). Neoadjuvant treatment was given to locally advanced tumors. Histological diagnosis was confirmed by surgery core-needle biopsy or frozen section during surgery. SLNBs were performed using blue dye and radiocolloid injections. All patients received a lymphoscintigraphy on the day of surgery. The dose of the injected radioisotope was 10-12 MBq (on the day of surgery). Patients were surgically treated by either total mastectomy or breast-conserving surgery. ALND was performed for Level I and II LNs if any macrometastases or micrometastases in SLN were detected in the frozen section analysis. Multifocal breast cancer is defined as a case in which multiple invasive foci existed in the same quadrant, and multicentric cancer was defined as one in which

the multiple invasive lesions were interspersed in the pleural quadrants. Treatment decision making was made in a multidisciplinary tumor board setting attended by surgeons, medical oncologists, and radiation oncologists specializing in breast cancer ER, PR, and HER2 receptor statuses were established on the resected primary tumor or on the core biopsy sample. PR and ER statuses were assessed by Allred scores, with an Allred score of 3 or more indicating ER or PR positivity (14, 15). HER2 expression was examined by immunohistochemical (IHC) analysis. A gene amplification assay using fluorescence in situ hybridization was used in cases where it was difficult to decide the HER2 status by IHC. The mean survival duration and cause of mortality were obtained from the population registry information. Statistical Package for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as means and standard deviations (median and minimum-maximum where necessary). Chi Fisher test statistics were used to compare categorical variables. In the comparison of continuous measurements between the groups, the distributions were controlled and Student T test was used for the parameters that normally distributed according to the number of variables. Mann-Whitney U test was used for the parameters not showing normal distribution. Kaplan-Meier analysis and Log Rank test were used for survival analysis. Statistical significance level was taken as 0.05 in all tests. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Before the operation, patients were informed about the operation and a written consent was obtained.

Invasive ductal carcinoma (IDC), invasive lobular carcinoma, rare non-invasive tumors and patients whose data were not available were excluded from the study.

Results

42 patients participated in our study. Group 1 (mix mucinous) consisted of 7 patients, and Group 2 (other rare tumors) consisted of 35 patients. The subtypes in Group 2 were papillary (n=21), pure mucinous (n=10) and tubular (n=4). There were no statistically significant differences between Group 1 and Group 2 in terms of the age of patients, estrogen receptor status, history of oral contraceptive use, family history of breast cancer, radiological BI-RADS, tumor localization, multifocality, neoadjuvant therapy, surgical treatment method, tumor diameter, pathological lymph node number, pathological stage, postoperative duration of stay, postoperative radiotherapy, chemotherapy, endocrine therapy and targeted treatment (Table 1).

Progesterone Receptor Positivity was found to be significantly higher in Group 2 patients than in Group 1 patients ($p=0.005$, $p<0.05$) (Table 1). Comorbid diseases were found to be statistically significantly higher in Group 1 than in Group 2 patients ($p=0.038$, $p<0.05$) (Table 1).

The rate of patients with breastfeeding history in Group 2 was found to be significantly higher than the patients in Group 1 ($p=0.048$, $p<0.05$) (Table 1). In the history of surgery variable, the patients in Group 2 had a significantly higher rate of appendectomy, TAH + BSO (total abdominal hysterectomy with bilateral salpingo-oophorectomy) and those without any surgical history than those in Group 1 ($p=0.031$, $p<0.05$). Multicentricity rates in the tumors of the patients in Group 1 were found to be statistically significantly higher than the patients in Group 2 ($p=0.024$, $p<0.05$).

Table 1. Patient, tumor, and treatment characteristics

Measurements		Group 1 n: 7	Group 2 n: 35	p*
Age (min-max)		56.7+11.6 (38-73)	56.6+12.3 (34-85)	0.982
Estrogen	Negative	0 (0.0)	2 (5.7)	0.691
	Positive	7 (100.0)	33 (94.3)	
Progesterone	Negative	6 (85.7)	9 (25.7)	0.005
	Positive	1 (14.3)	26 (74.3)	
Her2/neu	Negative	7 (100.0)	25 (71.4)	0.125
	Positive	0 (0.0)	10 (28.6)	
Comorbidity	No comorbid disease	2 (28.6)	24 (68.6)	0,038
	Singular disease	4 (57.1)	5 (14.3)	
	Double disease	1 (14.3)	6 (17.1)	
Oral contraceptive	Yes	0 (0.0)	4 (11.4)	0.468
	No	7 (100.0)	31 (88.6)	
Breastfeeding history	Yes	4 (57.1)	32 (91.4)	0.048
	No	3 (42.9)	3 (8.6)	
Family history	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	
Surgical history	Appendectomy	0 (0.0)	1 (2.9)	0.031
	BCS	1 (14.3)	0 (0.0)	
	TAH+BSO	1 (14.3)	6 (17.1)	
	Total Thyroidectomy	1 (14.3)	0 (0.0)	
	None	4 (57.1)	28 (80.0)	
Pre-op Imaging BI-RADS	3	1 (14.3)	1 (2.9)	0.136
	4	0 (0.0)	1 (2.9)	
	4A	2 (28.6)	6 (17.1)	
	4B	0 (0.0)	1 (2.9)	
	4C	0 (0.0)	18 (51.4)	
	5	4 (57.1)	8 (22.9)	
Localization	Bilateral	0 (0.0)	1 (2.9)	0.800
	Right	3 (42.9)	18 (51.4)	
	Left	4 (57.1)	16 (45.7)	
Multicentricity	Yes	2 (28.6)	0 (0.0)	0.024
	No	5 (71.4)	35 (100.0)	
Multifocality	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	
Neoadjuvant	Yes	0 (0.0)	2 (5.7)	0.691
	No	7 (100.0)	33 (94.3)	
Surgery	Mastectomy	4 (57.1)	9 (25.7)	0.118
	BCS	3 (42.9)	26 (74.3)	
Tumor diameter	T1	2 (28.6)	14 (40.0)	0.170
	T2	3 (42.9)	19 (54.3)	
	T3	2 (28.6)	2 (5.7)	

Table 1. Patient, tumor, and treatment characteristics (continued)

Measurements		Group 1 n: 7	Group 2 n: 35	p*
Lymph nodes	N0	5 (71.4)	28 (80.0)	0.152
	N1	1 (14.3)	6 (17.1)	
	N2	0 (0.0)	1 (2.9)	
	N3	1 (14.3)	0 (0.0)	
Stage	1A	2 (28.6)	10 (28.6)	0.603
	2A	3 (42.9)	20 (57.1)	
	2B	1 (14.3)	4 (11.4)	
	3A	1 (14.3)	1 (2.9)	
Postoperative duration of stay ((Mean+SD)(min-max)		3.0+2.2 (2-8)	2.4+1.0 (2-6)	0.323
Postoperative Radiotherapy	Yes	6 (85.7)	29 (82.9)	0.670
	No	1 (14.3)	6 (17.1)	
Postoperative Chemotherapy	Yes	3 (42.9)	6 (17.1)	0.155
	No	4 (57.1)	29 (82.9)	
Postoperative Endocrine treatment	Yes	4 (57.1)	16 (45.7)	0.444
	No	3 (42.9)	19 (54.3)	
Postoperative Targeted treatment	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	

BCS: Breast-conserving surgery; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; SD: Standard deviation

Table 2. Patient, tumor, and treatment characteristics, Group 2 subtypes

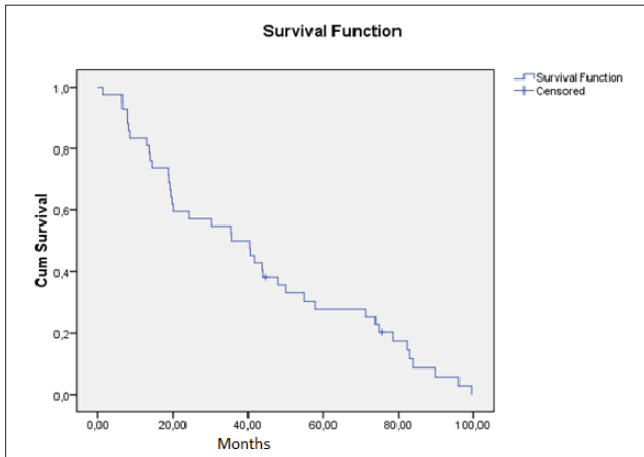
Measurements		Papillary (n: 21)	Pure Mucinous (n: 10)	Tubular (n: 4)	p*
Age (min-max)		57.7+12.3 (38-85)	52.6+13.0 (34-76)	60.5+10.5 (51-72)	0.452
Estrogen	Negative	2 (9.5)	0 (0.0)	0 (0.0)	0.493
	Positive	19 (90.5)	10 (100.0)	4 (100.0)	
Progesterone	Negative	8 (38.1)	1 (10.0)	0 (0.0)	0.113
	Positive	13 (61.9)	9 (90.0)	4 (100.0)	
Her2/neu	Negative	13 (61.9)	9 (90.0)	3 (75.0)	0.266
	Positive	8 (38.1)	1 (10.0)	1 (25.0)	
Comorbidity	No comorbid disease	13 (61.9)	8 (80.0)	3 (75.0)	0.676
	Singular disease	3 (14.3)	1 (10.0)	1 (25.0)	
	Double disease	5 (23.8)	1 (10.0)	0 (0.0)	
Oral contraceptive	Yes	3 (14.3)	0 (0.0)	1 (25.0)	0.335
	No	18 (85.7)	10 (100.0)	3 (75.0)	
Breastfeeding history	Yes	20 (95.2)	8 (80.0)	4 (100.0)	0.297
	No	1 (4.8)	2 (20.0)	0 (0.0)	
Family history	Yes	2 (9.5)	0 (0.0)	1 (25.0)	0.310
	No	19 (90.5)	10 (100.0)	3 (75.0)	
Surgical history	Appendectomy	0 (0.0)	1 (10.0)	0 (0.0)	0.371
	BCS	0 (0.0)	0 (0.0)	0 (0.0)	
	TAH+BSO	5 (23.8)	1 (10.0)	0 (0.0)	

Table 2. Patient, tumor, and treatment characteristics, Group 2 subtypes (continued)

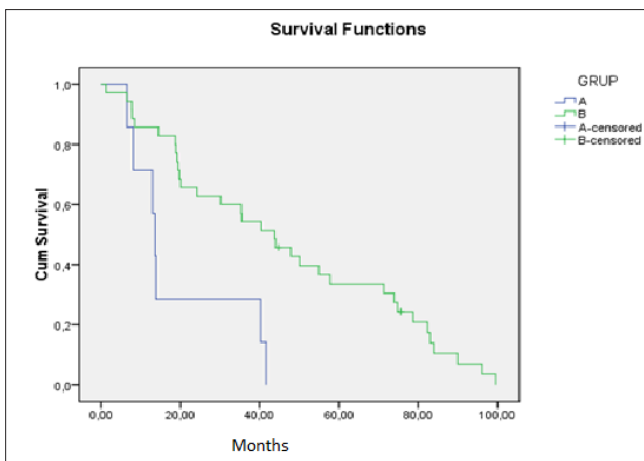
Measurements		Papillary (n: 21)	Pure Mucinous (n: 10)	Tubular (n: 4)	p*
Total Thyroidectomy	Total Thyroidectomy	0 (0.0)	0 (0.0)	0 (0.0)	0.632
	None	16 (76.2)	8 (80.0)	4 (100.0)	
Pre-op Imaging BI-RADS	3	0 (0.0)	1 (10.0)	0 (0.0)	0.632
	4	1 (4.8)	0 (0.0)	0 (0.0)	
	4A	4 (19.0)	2 (20.0)	0 (0.0)	
	4B	0 (0.0)	1 (10.0)	0 (0.0)	
	4C	10 (47.6)	5 (50.0)	3 (75.0)	
	5	6 (28.6)	1 (10.0)	1 (0.0)	
	5	6 (28.6)	1 (10.0)	1 (0.0)	
Localization	Bilateral	1 (4.8)	0 (0.0)	0 (0.0)	0.775
	Right	12 (57.1)	4 (40.0)	2 (50.0)	
	Left	8 (38.1)	6 (60.0)	2 (50.0)	
Multifocality	Yes	1 (4.8)	2 (20.0)	0 (0.0)	0.297
	No	20 (95.2)	8 (80.0)	4 (100.0)	
Neoadjuvant	Yes	1 (4.8)	1 (10.0)	0 (0.0)	0.734
	No	20 (95.2)	9 (90.0)	4 (100.0)	
Surgery	Mastectomy	7 (33.3)	2 (20.0)	0 (0.0)	0.334
	BCS	14 (66.7)	8 (80.0)	4 (100.0)	
Tumor diameter	T1	5 (23.8)	5 (50.0)	4 (100.0)	0.053
	T2	14 (66.7)	5 (50.0)	0 (0.0)	
	T3	2 (9.5)	0 (0.0)	0 (0.0)	
Lymph nodes	N0	15 (71.4)	10 (100.0)	3 (75.0)	0.437
	N1	5 (23.8)	0 (0.0)	1 (25.0)	
	N2	1 (4.8)	0 (0.0)	0 (0.0)	
	N3	0 (0.0)	0 (0.0)	0 (0.0)	
Stage	1A	2 (9.5)	5 (50.0)	3 (75.0)	0.067
	2A	14 (66.7)	5 (50.0)	1 (25.0)	
	2B	4 (19.0)	0 (0.0)	0 (0.0)	
	3A	1 (4.8)	0 (0.0)	0 (0.0)	
Postoperative duration of stay ((mean+SD)(min-max))		2.6+1.3 (2-6)	2.1+0.3 (2-3)	2.2+0.5 (2-3)	0.364
Postoperative Radiotherapy	Yes	17 (81.0)	8 (80.0)	4 (100.0)	0.625
	No	4 (19.0)	2 (20.0)	0 (0.0)	
Postoperative Chemotherapy	Yes	3 (14.3)	3 (30.0)	0 (0.0)	0.348
	No	18 (85.7)	7 (70.0)	4 (100.0)	
Postoperative Endocrine treatment	Yes	8 (38.1)	5 (50.0)	3 (75.0)	0.378
	No	13 (61.9)	5 (50.0)	1 (25.0)	
Postoperative Targeted treatment	Yes	3 (14.3)	0 (0.0)	0 (0.0)	0.335
	No	18 (85.7)	10 (100.0)	4 (100.0)	

BCS: Breast-conserving surgery; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; SD: standard deviation

In subtype analysis in Group 2, there were no statistically significant differences in demographic characteristics, clinicopathological features, surgical treatment modality and oncological treatment selection in the subgroups (Table 2).



Graphic 1. Mean survival



Graphic 2. Survival in groups

Mean survival was 41.9 ± 4.6 (32.6-51.1) months in all patients (Graphic 1), and 19.5 ± 5.6 (8.5-30.5) months and 46.3 ± 5.2 (36.1-56.6) months ($p:0.002$) in Group 1 and Group 2, respectively, when they were evaluated separately (Graphic 2).

Discussion and Conclusion

Mucinous carcinoma of the breast is rare in clinical practice and includes approximately 4% (1% to 6%) of all invasive breast cancers. It is more common especially in the peri-menopausal and postmenopausal age groups (16). Pure mucinous tumors have a good prognosis. Mix mucinous cancers have a poor prognosis because of their clinical characteristics and survival characteristics, which are similar to those of (IDC). It is important to distinguish mix mucinous tumors from pure mucinous tumors and other rare types.

Axillary lymph node involvement remains as an important prognostic factor. Axillary lymph node positivity is reported in the literature as 20-53% in mix mucinous carcinoma, as 4-17% in pure mucinous carcinoma (9, 17-21), as 3-18% in tubular carcinoma (19, 22, 23) and as 11% in papillary carcinoma (24). In our series, it was 29% for mix mucinous patients. When we evaluated the other rare tumors together, it was 20%. When we evaluated them separately, it was 0% in pure mucinous carcinoma, 25% in tubular carcinoma and 28.6% in papillary carcinoma. The lymph node involvement of mix mucinous tumors in our series were similar to that of papillary carcinoma.

In the treatment of mixed mucinous breast carcinoma and other rare tumors of the breast, the primary treatment protocol is surgery with postoperative adjuvant therapy. We performed mastectomy on 57% of the patients in Group 1, and 25.7% of the patients in Group 2. In our series, multicentricity, tumor diameter and patient request played a part in the decision of mastectomy. While no patient received neoadjuvant treatment in the mix mucinous group, 2 patients in the other group received it. Axillary lymph node involvement and tumor size played a role in the selection of neoadjuvant treatment. Adjuvant therapies after mastectomy were planned considering the recommendations of St. Gallen (25).

Radiotherapy was given to all patients after breast-conserving surgery, and axillary lymph node involvement and tumor size were affected in patients receiving radiotherapy after mastectomy. Adjuvant endocrine therapy is indicated for hormone responsive tumors. Almost all mucinous carcinomas are positive for estrogen and/or progesterone receptors, which means that hormonal therapy can be an effective treatment (26).

Human epidermal growth factor receptor (HER-2 / neu) is generally negative for mucinous tumors (18, 27). In our series, all of the mixed mucinous tumors were negative and 1 case was positive in pure mucinous tumors. When other rare tumors were examined, papillary carcinoma was 38% positive and tubular carcinoma was 25% positive. The presence of HER2 is important for agents targeting HER2, as in other breast cancers. While no patient received targeted therapy in the mix mucinous carcinoma group, 8.6% of the other rare tumors group received targeted treatment.

Di saverio (27) described tumor size as an independent prognostic indicator. Tumor diameter was reported in the literature to be above 5cm in 48% of mix mucinous tumors and in 22% of pure mucinous tumors. Tumor diameter in mix mucinous tumors was greater than pure mucinous tumors and other rare tumors, in many series (17, 28). In our series, there were 2 patients with a tumor diameter above 5 cm in the mix mucinous group, and the tumor diameter was not greater than 5 cm in any patient in the pure mucinous group.

In comparison of radiological imaging methods in literature, it has been reported that in mucinous tumors with mix pattern, BI-RADS 5 is more predominant than in pure and other types (29). In our series, 5 patients with mix mucinous tumor, 1 patient with pure mucinous tumor, and 6 patients with papillary carcinoma were BI-RADS 5.

Pure mucinous carcinoma of the breast and other rare tumors have a favorable prognosis because of low lymph node metastases, small tumor diameter and high hormone receptor positivity. Mix mucinous breast cancer has a worse prognosis because of their high incidence, large tumor size, high axillary lymph node metastases. Rare pathological types of breast cancer can have favorable outcomes when treated with necessary oncological principles.

Our study has several limitations. The major limitations of this study are the retrospective design and the small number of selected patients in each group.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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