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**Original Research:**

# Investigation of The Differences of Breast Cancer Molecular Subtypes in Radiological and Histopathological Parameters and their Effects on Lymphovascular İnvasion

**{ Short title:** Differences in breast cancer molecular subtypes}

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**Abstract:**

Introduction: Breast cancer has heterogeneous tumor biology. Therefore, breast cancer is divided into molecular subtypes. However, molecular subtypes also show heterogeneity within themselves. In our study, we compared whether there were radiological and pathological differences between breast cancer molecular subtypes.

Methods: The data of 569 patients operated on for breast cancer in our General Surgery clinic during an 8-year period were analyzed retrospectively. After dividing the patients into groups consisting of molecular subtypes, their radiological and pathological findings were compared.

Results: According to the molecular classification of breast cancer, 47.6% of the patients were in the luminal A group, 23.9% in luminal B, 7.7% in HER2-enriched, and 12% in TN, and 8.8% in normal-like groups. DCIS and LCIS were significantly less common in the TN group than in the others (p=0.015). Tumor diameter and grade were considerably higher in the normal-like, HER2-enriched, and TN groups than in the other groups (p<0.001, p<0.001). LVI was significantly lower in luminal A and significantly higher in luminal B (p<0.001). Mortality was significantly higher in the luminal B and TN groups than in the other groups (p = 0.029).

Conclusion: The addition of the basal-like group when classifying breast cancer into molecular subtypes showed histopathological differences. More studies are needed to investigate its effects on treatment and prognosis.

**Keywords:** Breast cancer, Molecular subtype, Genotype, Immunohistochemistry, Survival

**Introduction:**

Breast cancer is the most common type of cancer in women and is the second most important cause of cancer-related death in women (1). While new breast cancer is diagnosed in 125.1 out of 100,000 women in the United States (USA), Breast cancer causes 19.9 cancer-related deaths per 100,000 women (1). Furthermore, according to 2017 statistics, a woman's lifetime risk of developing breast cancer is 12.4%, which shows that one out of every eight women will be diagnosed with breast cancer (2). In 2020, 276,480 women in the United States received a breast cancer diagnosis, and 42,170 died. (3). According to the 2018 statistics of the International Agency for Research on Cancer, 2.1 million new patients were diagnosed with breast cancer (4). Breast cancer can develop from mammary lobules (milk glands), ducts that connect these lobules to the nipple (milk ducts), or from other cells in the breast (5). Risk factors include female gender, advanced age, family history, personal history of breast disease or cancer, and inherited genes that increase cancer risk. Radiation exposure, early menarche, late menopause, obesity, postmenopausal hormone therapy, alcohol use, and never getting pregnant or becoming pregnant at an older age are also risk factors. Histological parameters used in the management and treatment of breast cancer, tumor size, axillary lymph node metastasis, histological grade, lymphovascular invasion, hormone receptors such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status are the most important prognostic factors (8-10). Breast cancer is a heterogeneous disease, and five different molecular subtypes have been defined. These molecular subtypes include luminal A, luminal B, HER2-enriched, triple-negative (TN), and normal-like groups (11,12). Today, the effect of dividing breast cancer into molecular subtypes on prognosis is controversial. For this reason, we aimed to compare breast cancer molecular subtypes with radiological and pathological findings, to reach helpful information that will affect clinical practice and patient prognosis.

**Methods:**

Seven hundred twenty-three patients with invasive breast cancer operated between April 1, 2010, and December 31, 2018, in Ankara Numune Training and Research Hospital and Ankara City Hospital General Surgery Clinic were included in the study. One hundred fifty-four patients were excluded from the study due to a lack of data. The patient's age, ER, PR, HER2, lymphovascular invasion status, axillary lymph node metastasis status, multifocality status, presence of DCIS or LCIS, tumor diameter, histopathological type, histopathological grade, and score of the tumor were recorded from the retrospective file scan of 569 patients.

In this study, breast cancer was divided into different subgroups according to various gene expressions. Luminal group A breast cancers are hormone receptor-positive (estrogen receptor and/or progesterone receptor positive), HER2 negative, and low Ki-67 proliferation index. Cancers in the luminal subgroup A are histopathologically low grade. Luminal group B breast cancers are hormone receptor-positive (estrogen receptor and/or progesterone receptor positive), and Ki-67 proliferation index is high, HER2 positive or HER2 negative. HER2-enriched breast cancers are hormone receptor negative (estrogen receptor and progesterone receptor negative) and HER2 positive. TN (Basal-like) breast cancers are hormone receptor negative (estrogen receptor and progesterone receptor negative) and HER2 negative. BRCA1 gene mutations are more common in this group of women. Normal like breast cancers resemble luminal A breast cancers. It is hormone receptor-positive (estrogen receptor and/or progesterone receptor positive), HER2 negative, and has a low Ki-67 proliferation index.

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After immunohistochemical evaluation, nuclear staining for ER, PR, Ki-67 index and membranous staining for HER2 were accepted as positive findings. The HER2 score was 0, 1+, 2+, and 3+ according to staining intensity and membranous persistence. In cases where the HER2 score was 2+, DNA fluorescence in situ hybridization (FISH) results were evaluated. Patients with HER2 overexpression were recorded as 3+. Patients with a Ki-67 proliferation index above 14 were considered Ki-67 positive.

**Statistical analysis:**

Statistical Package for Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics, frequency, and percentages of categorical variables are reported. Using the Chi-square test for categorical variables, we examined the relationship between molecular subtypes, age, tumor size, histopathological subtype, grade, presence of carcinoma in situ foci, multifocality, and lymphovascular invasion, and lymph node metastasis status at diagnosis. Post-hoc analysis was performed with Bonferroni correction to determine where the significant difference between the groups originated. The Kaplan-Meier method was used to calculate the mean overall survival. Cox proportional hazards regression analysis was performed to estimate breast cancer-specific mortality hazard ratios (HR). The results were considered statistically significant if the P value was <0.05. The study was approved by Ankara City Hospital 1. Clinical Research Ethics Committee (Decision no: E1-20-1292, date: 11.11.2020).

**Table 1. Classification of breast cancer patients according to their immunohistochemically staining status and Luminal classification.**

| **Immunohistochemically Staining status** | | **Frequency** | **Percent** |
|---|---|---|---|
| **ER** | Negative | 123 | 21.62 |
| | Positive | 446 | 78.38 |
| **PR** | Negative | 124 | 21.79 |
| | Positive | 445 | 78.21 |
| **HER2** | Negative | 467 | 82.07 |
| | Positive | 102 | 17.93 |
| **Ki-67** | <%15 | 399 | 70.12 |
| | ≥%15 | 170 | 29.88 |
| **Luminal Classification** | | | |
| **Luminal A** | | 271 | 47.6 |
| **Luminal B** | | 136 | 23.9 |
| **HER2-enriched** | | 44 | 7.7 |
| **Triple-negative** | | 68 | 12.0 |
| **Normal-like** | | 50 | 8,8 |
| **Total** | | 569 | 100 |

**Table 2. Histopathological findings of breast cancer patients according to the Luminal classification.**

| | | | Luminal Classification | | | | | *p* value |
|---|---|---|---|---|---|---|---|---|
| | | | **Luminal A** | **Luminal B** | **HER2-enriched** | **Triple-negative** | **Normal-like** | |
| **DCIS or LCIS** | **No** | N | 89 | 40 | 14 | 36 | 17 | 0.015 |
| | | % | 45.41 | 20.41 | 7.14 | 18.37 | 8.67 | |
| | **Yes** | N | 182 | 96 | 30 | 32 | 33 | |
| | | % | 48.79 | 25.74 | 8.04 | 8.58 | 8.85 | |
| **Tumor Size** | **<2 cm** | N | 140 | 36 | 13 | 18 | 13 | <0.001 |
| | | % | 63.64 | 16.36 | 5.91 | 8.18 | 5.91 | |
| | **2-5 cm** | N | 130 | 97 | 30 | 45 | 35 | |
| | | % | 38.58 | 28.78 | 8.90 | 13.35 | 10.39 | |
| | **>5 cm** | N | 1 | 3 | 1 | 5 | 2 | |
| | | % | 8.33 | 25 | 8.33 | 41.67 | 16.67 | |
| **GRADE** | **Low** | N | 115 | 18 | 6 | 6 | 0 | <0.001 |
| | | % | 79.31 | 12.41 | 4.14 | 4.14 | 0 | |
| | **Intermediate** | N | 156 | 77 | 10 | 24 | 8 | |
| | | % | 56.73 | 28 | 3.64 | 8.73 | 2.91 | |
| | **High** | N | 0 | 41 | 28 | 38 | 42 | |
| | | % | 0 | 27.52 | 18.79 | 25.50 | 28.19 | |
| **LVI** | **No** | N | 200 | 61 | 26 | 42 | 29 | <0.001 |
| | | % | 55.87 | 17.04 | 7.26 | 11.73 | 8.10 | |
| | **Yes** | N | 71 | 75 | 18 | 26 | 21 | |
| | | % | 33.65 | 35.55 | 8.53 | 12.32 | 9.95 | |
| **Lymph Node Metastasis** | **No** | N | 191 | 62 | 25 | 42 | 27 | <0.001 |
| | | % | 55.04 | 17.87 | 7.20 | 12.10 | 7.78 | |
| | **Yes** | N | 80 | 74 | 19 | 26 | 23 | |
| | | % | 36.04 | 33.33 | 8.56 | 11.71 | 10.36 | |
| **Total** | | N | 271 | 136 | 44 | 68 | 50 | |
| | | % | 47.63 | 23.90 | 7.73 | 11.95 | 8.79 | |

**Table 3. Stage status of breast cancer patients according to Luminal classification**.

| | | | Luminal Classification | | | | | *p* value |
|---|---|---|---|---|---|---|---|---|
| | | | **Luminal A** | **Luminal B** | **HER2-enriched** | **Triple-negative** | **Normal-like** | |
| **Stage** | **Stage I** | N | 134 | 33 | 14 | 17 | 15 | <0.001 |
| | | % | 62.9 | 15.5 | 6.6 | 8 | 7 | |
| | **Stage IIa** | N | 89 | 34 | 17 | 33 | 15 | |
| | | % | 47.3 | 18.1 | 9 | 17.6 | 8 | |
| | **Stage IIb** | N | 28 | 30 | 5 | 10 | 7 | |
| | | % | 35 | 37.5 | 6.3 | 12.5 | 8.8 | |
| | **Stage IIIa** | N | 20 | 28 | 4 | 5 | 8 | |
| | | % | 30.8 | 43.1 | 6.2 | 7.7 | 12.3 | |
| | **Stage IIIb** | N | 0 | 0 | 1 | 1 | 0 | |
| | | % | 0 | 0 | 50 | 50 | 0 | |
| | **Stage IIIc** | N | 0 | 11 | 3 | 2 | 5 | |
| | | % | 0 | 52.4 | 14.3 | 9.5 | 23.8 | |
| **Total** | | N | 271 | 136 | 44 | 68 | 50 | |
| | | % | 47.6 | 23.9 | 7.7 | 12 | 8.8 | |

**Table 4. Mortalitiy according to Luminal classification**

| | | | Discharge Status | | P value |
|---|---|---|---|---|---|
| | | | **Survive** | **Death** | |
| **LUMINAL** | Luminal A | N | 257 | 20 | 0.029 |
| | | % | 92.8 | 7.2 | |
| | Luminal B | N | 138 | 18 | |
| | | % | 88.5 | 11.5 | |
| | HER2-enriched | N | 39 | 1 | |
| | | % | 97.5 | 2.5 | |
| | Triple-Negative | N | 47 | 11 | |
| | | % | 81 | 19 | |
| | Normal-like | N | 34 | 4 | |
| | | % | 89.5 | 10.5 | |
| **Total** | | N | 515 | 54 | |
| | | % | 90.5 | 9.5 | |

**Figures**

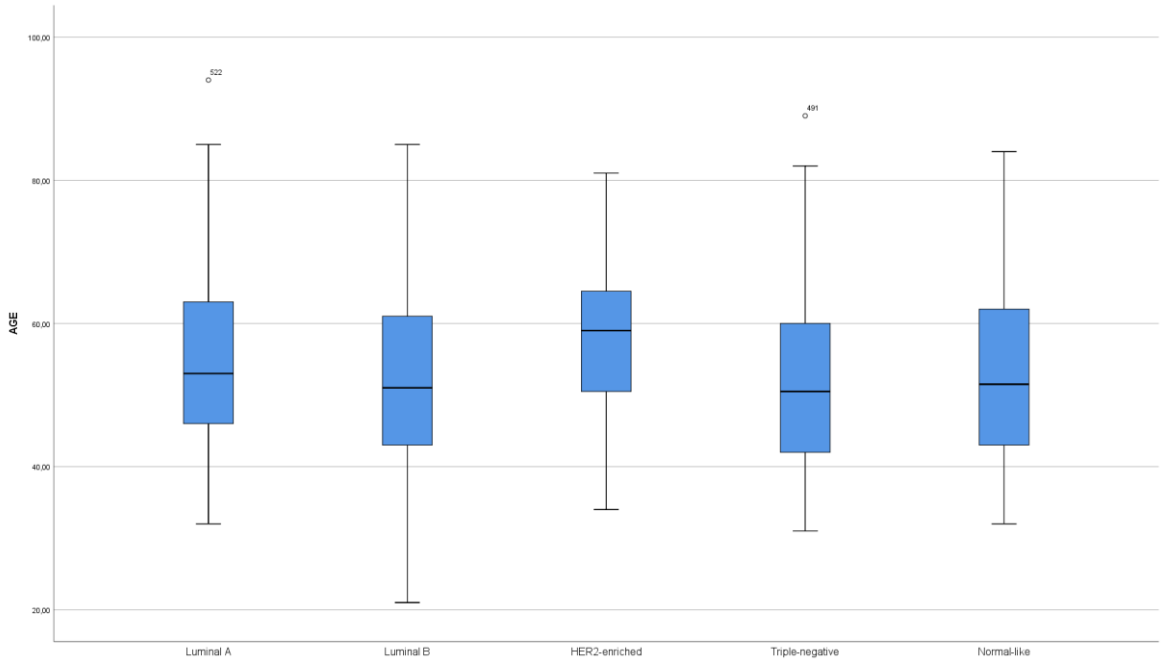


**Fig. 1. Luminal classification patient age distribution**

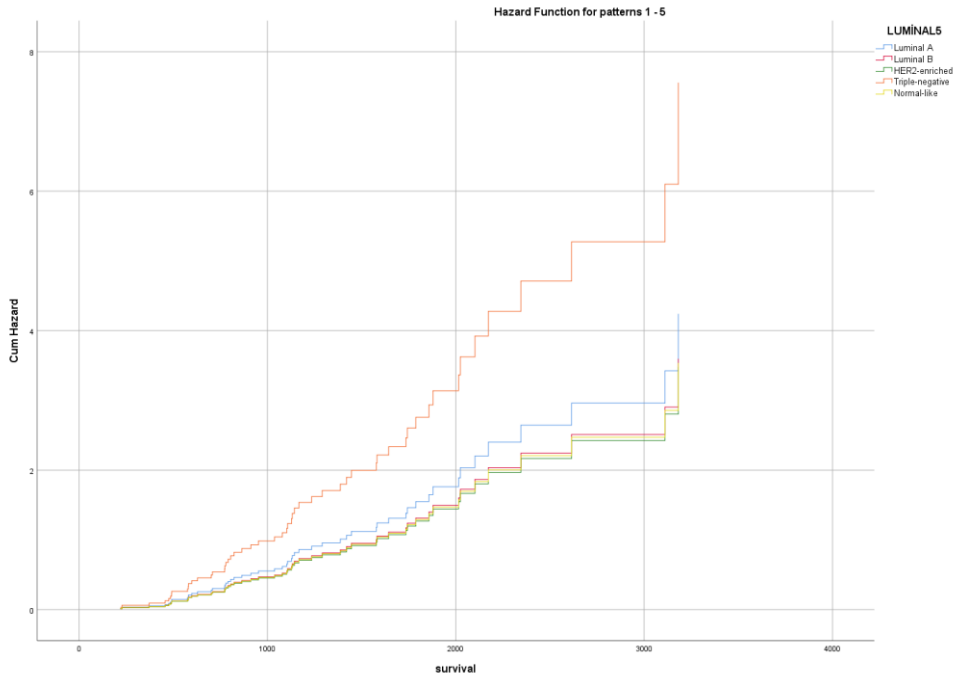


**Fig. 2. Luminal classification death**

**Results:**

The mean age of the patients was 54.09±12.65 (min.:21, median: 52, and max.:94) years. The mean age of the patients in the luminal B and TN groups was lower (Fig. 1). The mean follow-up period was 5.07±2.33 years, and the mean survival of the patients who died was 3.44±2.1 years. It was determined that 56.8% of the patients (323) underwent BCS, (100) 17.6% mastectomy, and 25.7% (146) MRM surgery. Only SLND was performed in 70.97% of patients (433), and ALND was performed in 25.34% (151). According to the immunohistochemical staining results of breast cancer patients, ER was 78.38%, PR was 78.21%, HER2 was 17.93%, and Ki-67 was 29.88% positive (Table 1). According to the molecular classification of breast cancer, 47.6% were in luminal A, 23.9% in luminal B, 7.7% in HER2-enriched, 12% in TN, and 8.8% in normal-

like groups. DCIS and LCIS were significantly less common in the TN group due to post-hoc analysis when molecular subtypes were compared (p=0.015) (Table 2). Tumor locations follow, 3.7% were in the central region, 7.2% in the lower inner quadrant, 12.3% in the upper inner quadrant, 13.5% in the lower outer quadrant, and 63.3% in the upper outer quadrant. The location of the tumor and molecular subtypes were compared, and there was no significant difference (p=0.831). In 26% of the patients, breast cancer was detected in more than one part of the breast, while in a single site in 74%. No statistically significant differences were observed in comparing molecular subtypes and multifocality (p=0.128). When tumor diameter and molecular subtypes were compared, tumor diameter was significantly higher in normal-like, HER2-enriched, and TN groups (p<0.001). Patients with high tumor grade were significantly more common in normal-like, HER2-enriched, and TN groups (p<0.001) comparing molecular subtypes according to tumor grade. In comparing LVI and molecular subtypes, LVI was significantly lower in luminal A and significantly higher in luminal B (p<0.001). When the molecular subtypes were compared in terms of lymph node metastasis, it was found that while there was significantly less metastasis in the luminal A group, it was found that it metastasized significantly more in the luminal B group (p<0.001). When the molecular subtypes were compared according to breast cancer stage, the difference between the groups was found to be significant because the patients in the luminal group B were in stage IIIa, and the patients in the HER2-enriched and TN groups were in stage IIa (p< 0.001) (Table 3). Mortality was significantly higher in the luminal B and TN groups (p = 0.029) (Table 4). The mortality hazard ratios (HR) for breast cancer molecular subtypes were calculated, and no statistically significant difference was found between the groups (p=0.476). A statistically significant difference was found between the mean survival curves of the TN and other groups with the Kaplan-Meier test (Log Rank p=0.006). However, when the TN group was compared with the other groups, HR was higher in the TN group than in the others (Fig. 2). However, the Cox-Regression result was not statistically significant (HR: 0.51, CI 95%, 0.26-1.02, p = 0.057).

**Discussion:**

ER and PR are receptors that stimulate the growth of normal and neoplastic breast epithelium. ER, and PR positive tumors are low grade and less aggressive. ER or PR positive tumors constitute 72.5%-79% of breast cancers (13,14). (16). HER2 overexpression indicates an aggressive clinical course and poor prognosis. It is recommended that ER and PR tests be considered positive if there are at least 1% positive invasive tumor nuclei in the sample (15). In cases where HER2 is 2+, DNA fluorescence in situ hybridization (FISH) should be done.

In our study, patients with breast cancer were divided into five molecular subtypes. They consist of luminal A, luminal B, HER2-enriched, triple negative, and normal-like subtypes. The normal-like type has started being used recently. It has a high tumor grade, non-epithelial tumor cell content, and adipose tissue components. It has a slightly worse prognosis than patients with Luminal A breast cancer (17-19. Some authors see it as tumor tissue contaminated by normal breast tissue (20,21).

Jenkins EO et al. reported that the incidence of luminal A and luminal B tumors increases with age (22). Durbecq V et al. reported that TN and HER2 positive patients are seen more frequently in young patients, luminal A subtype with a less aggressive course is observed in patients over 50 years of age, and luminal B tumors develop in patients over 70 years of age (23). In their study, Pandit P et al. showed that the luminal A subtype increases with age, and the luminal B subtype is observed in younger patients, although not as much as the TN subtype (24). Similar to previous studies, our study also observed the TN subtype in younger patients. Unlike the study of Durbecq V et al., our patients with the luminal B subtype had a lower mean age.

Howlader N et al. reported hormone receptor positivity as 72.7%, HER2-enriched as 4.6%, and TN as 12.2% in their study (25). In our research,

hormone receptor positivity was 78.38%, and our results were similar to previous studies (25-27). It has been reported that HER2-positive tumors constitute 14.9-20% of breast cancer subtypes (25-27). In our study, it was 17.93%. Ki-67 positivity was 29-37% (27). In our research, Ki-67 positivity was 29.88%, consistent with previous studies.

Li J et al. reported that the frequency of luminal A, luminal B, HER2-positive luminal B, HER2-enriched, and triple-negative subtypes was 35.6%, 22.5%, 13.1%, 13.7%, and 15.2%, (28). Saliha B et al. reported the frequency of luminal A, luminal B, HER2-enriched, and triple-negative subtypes as 44.3%, 24.6%, 11.8% and 11.3%, respectively (29). Zhou W et al. reported that the frequency of luminal A, luminal B, HER2-enriched, and triple-negative subtypes were 48.8%, 26.1%, 16%, and 7.1%, respectively (30). In our study, the frequency of luminal A, luminal B, HER2-enriched and triple negative subtypes were 47.6%, 23.9%, 7.7%, and 12%, respectively, in line with the literature. Although the association between TN breast cancer and DCIS is less common, it has been reported that the risk of local recurrence of breast cancer is higher in patients followed for more than ten years (30,31).

Desai AA et al. reported that tumors located in the areola, central breast, and axillary tail in patients with invasive breast cancer have the highest risk of axillary lymph node positivity regardless of patient age, tumor grade, and biological subtype, histology, and size (32). Lale A et al. reported that tumor localization and multifocality/multicentricity were not significant in the development of axillary lymph node metastasis in patients with early-stage breast cancer. (33). However, there is no study in the literature showing the relationship between breast cancer molecular subtype and tumor localization and multicentricity. In our study, there is no difference between the tumor's location in the breast and the molecular subtypes.

Al-Thoubaity FK reported that HER2-positive and TN tumors from breast cancer molecular subtypes showed higher histological grade and larger tumor size at the time of diagnosis (34). Alnegheimish NA et al. reported that HER2 positive and TN patients at the diagnosis had a larger tumor size and a higher histological grade (35). Similarly, our study found significantly larger tumor diameter and higher histological grade in normal-like, HER2-enriched, and TN subgroups.

Morkavuk SB et al. reported that LVI was significantly higher in HER2-negative luminal B and TN subgroups (10). Chas M et al. published data showing that lymphovascular invasion is higher in HER2 positive, luminal B and TN subgroups (36). In our study, when LVI and molecular subtypes were compared, we found that LVI was significantly lower in luminal A and significantly higher in luminal B.

Zhou W et al. reported that the luminal B subgroup showed a higher rate of NSLN metastasis rate than the other subgroup (37). In our study, axillary lymph node metastases were also significantly higher in the luminal B subgroup.

Howlader N et al. reported that patients in the luminal A subgroup had the best survival patterns while TN patients had the worst (25). Fallahpour S et al. reported that the highest survival was in luminal A, and the worst was in the TN subtype. Still, the patient's age and the disease's stage at diagnosis also negatively affected survival in the form of a dose-response effect (38). In our study, mortality was significantly higher in luminal B and TN groups when age and disease stage at the diagnosis was not considered. HR was 0.5 times higher in the TN subgroup compared to the other groups.

The shortcomings of our study are that it was a retrospective study, whether patients had neoadjuvant chemotherapy, and the response was unknown. Its strengths are that it was conducted on a large group of patients who were followed up regularly in our hospital.

**Conclusion:**

The use of molecular subtypes to understand the biology of breast cancer and the separation of the basal-like group, which has different prognostic features from the luminal A group, may be useful in evaluating the treatment and survival of

patients. Further studies are needed on this subject in the prospective, large series.

**Authors Contribution**

SK conceived, designed and did statistical analysis & editing of manuscript

SK, CC, BÇ, BAÖ, MÖY did data collection and manuscript writing

AMT, EM, SK, FS, MÖY, BK did review and final approval of manuscript

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