Metaplastic Breast Cancer: Mesenchymal Subtype Has Worse Survival Outcomes

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Key words
Breast neoplasms · Survival rate · Disease-free survival · Metaplastic carcinoma · Overall survival

Abstract

Background: Metaplastic breast carcinoma (MBC) is a rare type of breast cancer that accounts for 0.2–1% of all breast cancers. To date, there are only few institutional studies comparing survival rates between different subtypes. In this retrospective cohort study, we aim to evaluate factors affecting survival rates of different subtypes of MBC.

Methods: This retrospective cohort study observed 118 nonmetastatic MBC patient records extracted from 15,244 breast cancer cases between December 2000 and December 2020. In order to analyze factors affecting survival rates of mesenchymal subtype of MBC, all cases are classified as mesenchymal (n = 45) and other (n = 48). Twenty-five cases could not be subclassified due to the missing data. Univariate and multivariate logistic regression analyses were performed to define factors associated with survival rates.

Results: Of the 15,244 cases, 118 (0.8%) were nonmetastatic MBC patient records extracted from 15,244 breast cancer cases between December 2000 and December 2020. In order to analyze factors affecting survival rates of mesenchymal subtype of MBC, all cases are classified as mesenchymal (n = 45) and other (n = 48). Twenty-five cases could not be subclassified due to the missing data. Univariate and multivariate logistic regression analyses were performed to define factors associated with survival rates. Results: Of the 15,244 cases, 118 (0.8%) were nonmetastatic MBC. 105 were triple negative and 12 were nonluminal HER2. There was no significant difference between mesenchymal and other subgroups for age, median tumor size, AJCC staging, and type of surgery. Of the five local recurrences with known subgroup, four of them had mesenchymal subtype. It is demonstrated that mesenchymal subtype was significantly associated with worse 5-year disease-free survival and disease-specific survival (HR: 2.35 [1.01–5.48], p = 0.049, and HR: 3.16 [1.06–9.47], p = 0.040 with 95% CI, respectively).

Conclusion: This study is one of the few studies presenting the survival outcomes of subtypes of MBCs. Nonetheless, it is the only study demonstrating that mesenchymal subtype had worse survival outcomes. Further studies are needed to determine the outcome of different subtypes of MBCs.

Introduction

Metaplastic breast carcinoma (MBC) is a rare type of breast cancer that accounts for 0.2–1% of all breast cancers [1]. It was first described in 1973 but recognized as a new breast cancer subtype by World Health Organization in 2000 [2]. It is basically described as squamous or mesenchymal differentiation of neoplastic epithelium to a nonglandular component and histologically classified as low-grade adenosquamous carcinoma, fibromatoses-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with heterologous mesenchymal differentiation and mixed metaplastic carcinoma [3]. Those subtypes including squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation are considered as the aggressive subtypes. They are more aggressive and more prone to make metastasis than invasive ductal type breast cancers including triple-negative breast cancer (TNBC) [4, 5]. It usually spreads hematogenously rather than lymphatically [6–8]. MBCs are generally triple negative (TN), and they are associated with higher tumor (T) stage and less nodal involvement at presentation [9].
In the recent literature, there is a lack of information about survival rates of different subtypes of MBC. To date, there are only few institutional studies comparing survival rates between different subtypes [10–12]. In this retrospective cohort study, we aim to evaluate factors affecting survival rates of different subtypes of MBC.

Materials and Methods

Patient Cohort and Data Collection

This retrospective cohort study is planned to evaluate patients with a pathologic diagnosis of MBC. A total of 15,244 breast cancer patient records between December 2000 and December 2020 were evaluated. Patients with American Joint Committee on Cancer (AJCC) stage IV diseases and missing data were excluded. Finally, 118 MBC patients were extracted from institutional database. This is an observational study. The Istanbul University Istanbul Faculty of Medicine Research Ethics Committee has confirmed that no ethical approval is required for this retrospective study.

Surgical procedure was planned as mastectomy or breast conserving surgery (BCS) depending on clinical presentation of the patient. Adjuvant or neoadjuvant therapies were individually decided in a multidisciplinary breast surgical oncology meeting. Chemotherapy (CT) regimens and radiotherapy (RT) procedure were decided concordant with up-to-date guidelines. Main CT regimen was anthracycline and alkylating agents like cyclophosphamide followed by taxanes. If the patient is human epidermal growth receptor-2 (HER2) positive, a monoclonal antibody like trastuzumab was administered.

Definitions and Statistical Analysis

Overall survival (OS) is defined as the length of time from the date of diagnosis to death from any cause or to date of last follow-up. Disease-free survival (DFS) is defined as the time from diagnosis until recurrence of T or death from any cause. Disease-specific survival (DSS) is defined as the length of time from the date of diagnosis to death from disease or to date of last follow-up. Loco-regional recurrence-free survival (LRFS) is defined as the length of time from the date of diagnosis to the development of new T in ipsilateral breast, chest, or regional lymph nodes.

WHO categorizes MBC into six subtypes: low-grade adenosquamous, fibromatosis-like metaplastic, spindle cell, squamous cell, metaplastic carcinoma with heterologous mesenchymal differentiation, and mixed metaplastic. Except low-grade adenosquamous and fibromatosis-like subtype, MBC is considered as an aggressive breast cancer [4]. Mesenchymal subtype of MBC is an aggressive T that is composed of an admixture of differentiated mesenchymal component (chondroid, osseous, rhabdomyoid, etc.) elements [1] (Fig. 1). In the 5th edition of WHO classification of Ts of the breast, mesenchymal metaplastic carcinoma is further subclassified into 3 categories: carcinoma with chondroid differentiation, carcinoma with osseous differentiation, and carcinoma with other types of mesenchymal differentiation [3]. In order to analyze factors effecting survival rates of mesenchymal subtype of MBC (n = 43), all cases are classified as mesenchymal (chondroid [n = 24], osseous [n = 10], other [n = 2], and unclassified [n = 9]) and other. In the other group (n = 48), there are squamous cell MBC (n = 43), spindle cell MBC (n = 3), and mixed type MBC (n = 2). Of the total 118 MBC cases, 25 cases that could not be sub-classified due to the missing data are not included in the analysis regarding subgroups.

To assess differences in categorical and continuous variables, χ² tests (Pearson χ², continuity correction, Fisher's exact test) and Mann-Whitney U test were used. Survival rates were analyzed using Kaplan-Meier method, and log-rank test was issued in order to analyze the effect of patient demographics and pathologic features on survival rates. Univariate and multivariate logistic regression analyses were performed to define factors associated with survival rates. All p values were two-sided, and a p value of <0.05 with a 95% confidence interval (CI) was considered as significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Windows software version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Of the 15,244 breast cancer patients recorded between December 2000 and December 2020, 118 (0.8%) were nonmetastatic MBC. Two patients with AJCC stage IV disease were excluded. Median age was 48 (27–84). Almost two-thirds of the patients were T2 without axillary involvement. Of those, 72 patients (61%) underwent BCS, whereas mastectomy was performed in the remaining cases (39%). All patients received systemic therapy, and 16 of them received neoadjuvant CT (NCT). Of the 117 cases with known receptor status, 105 were TN and 12 were nonluminal HER2. There were no cases with hormone receptor positivity (Table 1). As described before, metaplastic carcinomas were stratified as mesenchymal for 45 (48.4%) and other for 48 (51.6%). In the subgroup analysis, there was no statistical significant difference between mesenchymal and other subgroups for age, median T size, AJCC staging, and type of surgery (Table 2).
Median follow-up time was 57 months. 5-year OS is 80%. The DFS, DSS, and LRFS rates were 76.2%, 82.4%, and 93.5%, respectively. There were only seven local-regional recurrences, which two of them were chest wall and five of them were in breast. No axillary recurrence was observed in our series. Of the five local recurrences with known subgroup, four of them had mesenchymal subtype. Significant factors effecting DFS and DSS in univariate Cox regression analysis (Table 3) were further analyzed in multivariate Cox proportional hazard regression model (Table 4). The 5-year DFS was 69.3% versus 86.2%, DSS was 77.8% versus 88.2%, and LRFS was 91.6% versus 97.8% for mesenchymal versus other subtypes of MBC, respectively. Our results have demonstrated that mesenchymal subtype was significantly associated with worse 5-year DFS and DSS (hazard ratio [HR]: 2.35 [1.01–5.48], p = 0.049, and HR: 3.16 [1.06–9.47], p = 0.040 with 95% CI, respectively).

| Factors                  | Category       | n     | %    |
|--------------------------|----------------|-------|------|
| Median age               |                | 48 (27–84) |
| ≤40                      | 31             | 26.3  |
| >40                      | 87             | 73.7  |
| <50                      | 62             | 52.5  |
| ≥50                      | 56             | 47.5  |
| Median T diameter, mm    | 30 (8–140)     |       |
| pT stage                 |                |       |
| I                        | 25             | 21.2  |
| II                       | 73             | 61.9  |
| III                      | 17             | 14.4  |
| IV                       | 3              | 2.5   |
| pN stage                 |                |       |
| 0                        | 75             | 63.6  |
| I                        | 29             | 24.6  |
| II                       | 8              | 6.8   |
| III                      | 6              | 5.1   |
| pStage                   |                |       |
| I–IIA                    | 71             | 60.2  |
| IIB–IIC                  | 47             | 39.8  |
| Operation type           |                |       |
| BCS                      | 72             | 61.0  |
| Mastectomy               | 46             | 39.0  |
| Axillary surgery         |                |       |
| SLNB                     | 72             | 61.0  |
| SLNB + ALND              | 26             | 22.0  |
| ALND                     | 20             | 16.9  |
| NCT                      |                |       |
| Yes                      | 16             | 13.6  |
| No                       | 102            | 86.4  |
| Systemic treatment       |                |       |
| CT (+)/RT (−)            | 11             | 9.3   |
| CT (+)/RT (+)            | 107            | 90.7  |
| Grade                    |                |       |
| II                       | 3              | 2.5   |
| III                      | 115            | 97.5  |
| LVI                      |                |       |
| +                        | 78             | 66.1  |
| −                        | 40             | 33.9  |
| HER2 (n = 117)           |                |       |
| −                        | 105            | 89.7  |
| +                        | 12             | 10.3  |
| Molecular subtype (n = 117) |           |       |
| TN                       | 105            | 89.7  |
| Nonluminal HER2 (+)      | 12             | 10.3  |
| Median Ki67 score (%) (n = 96) | 70 (range, 20–90) |       |
| Metaplastic subtype (n = 93) |             |       |
| Mesenchymal              | 45             | 48.4  |
| Other                    | 48             | 51.6  |

BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CT, chemotherapy; RT, radiotherapy; LVI, lymphovascular invasion; HER2, human epidermal growth receptor-2; TN, triple negative.
**Discussion**

In the up-to-date literature, there is a lack of information about clinicopathologic features and survivals of different subtypes of MBC. Few studies only emphasize this topic [10–16]. Almost all of the studies give information solely about MBC or compare differences between MBC and TNBC [17–19]. In these studies [9, 20, 21], researchers determined that MBC is generally larger in T size and presents lower nodal involvement. Conversely, it is diagnosed at more advanced stages, has worse survival rates, and is more resistant to adjuvant therapies when compared to other subtypes of breast cancer. Additionally, MBCs are generally TN subtype. In this study, we do not compare MBC and TNBC. Alternatively, we aim to focus on factors effecting survival rates of different subtypes of MBCs and specifically comparing mesenchymal subtype and others.

There are prominent features that effects survival rates in different types of breast cancer. In a recent National Cancer Database (NCDB) analysis of 2,084 MBCs, higher T stage, nodal involvement, and lymphovascular invasion (LVI) are correlated with worse outcomes [9]. Moreover, MBC had worse unadjusted OS when compared with TNBC and other types of breast cancer regardless of clinical stage. Same in our study, higher T stage, nodal involvement, and LVI are significantly correlated with worse 5-year DFS and DSS (Table 3). A Surveillance, Epidemiology, and End Results (SEER) analysis by Schroeder et al. [22] demonstrated that HER2-positive MBCs are associated with better survival compared to TN MBCs in a multivariate Cox regression model. We did not identify any survival difference between TN and HER2-positive MBC subtypes.

**Table 2.** Demographic and pathologic features of cases depending on MBA subtypes (*n* = 93)

| Factors                | Category          | All *n* | Mesenchymal (*n* = 45) | Other (*n* = 48) | *p* value |
|------------------------|-------------------|---------|------------------------|------------------|-----------|
| Median age (range)     | All               | 93      | 46 (27–77)             | 49 (30–84)       | 0.224*    |
|                        | <50               | 41      | 17 (37.8)              | 24 (50.0)        | 0.328*    |
|                        | ≥50               | 52      | 28 (62.2)              | 24 (50.0)        |           |
| Median T size, mm      |                   | 30      | 31 (10–140)            | 30 (10–130)      | 0.966*    |
| pT                     | I–II              | 79      | 40 (88.9)              | 39 (81.3)        | 0.389*    |
|                        | III–IV            | 14      | 5 (11.1)               | 9 (18.8)         |           |
| pN                     | 0                 | 61      | 31 (68.9)              | 30 (62.5)        | 0.667*    |
|                        | I–III             | 32      | 14 (31.1)              | 18 (37.5)        |           |
| pStage                 | I–IIA             | 57      | 30 (66.7)              | 27 (56.3)        | 0.414*    |
|                        | IIB–IIC           | 36      | 15 (33.3)              | 21 (43.8)        |           |
| Surgery type           | BCS               | 57      | 28 (62.2)              | 29 (60.4)        | 0.999*    |
|                        | Mastectomy        | 36      | 17 (37.8)              | 19 (39.6)        |           |
| Axillary surgery       | SLNB              | 55      | 28 (62.2)              | 27 (56.3)        | 0.708*    |
|                        | SLNB + ALND/ALND  | 38      | 17 (37.8)              | 21 (43.8)        |           |
| NCT                    | Yes               | 9       | 4 (8.9)                | 5 (10.4)         | 0.999*    |
|                        | No                | 84      | 41 (91.1)              | 43 (89.6)        |           |
| Systemic treatment     | CT (+)/RT (−)     | 9       | 6 (13.3)               | 3 (6.3)          | 0.307*    |
|                        | CT (+)/RT (+)     | 84      | 39 (86.7)              | 45 (93.8)        |           |
| Grade                  | II                | 3       | 1 (2.2)                | 2 (4.2)          | 0.999*    |
|                        | III               | 90      | 44 (97.8)              | 46 (95.8)        |           |
| LVI                    | Yes               | 33      | 13 (28.9)              | 20 (41.7)        | 0.285*    |
|                        | No                | 60      | 32 (71.1)              | 28 (58.3)        |           |
| Molecular subtype (*n* = 92) | TN          | 87      | 44 (100.0)             | 43 (89.6)        | 0.057*    |
|                        | Nonluminal HER2 (+) | 5      | 0 (0.0)                | 5 (10.4)         |           |
| Mean Ki67 score (*n* = 96) |                   | 74      | 70.61±15.95            | 63.05±18.26      | 0.052*    |

BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; NCT, neoadjuvant chemotherapy; CT, chemotherapy; RT, radiotherapy; LVI, lymphovascular invasion; HER2, human epidermal growth receptor-2. *p > 0.05. * Mann-Whitney U test. b χ² test.
As WHO recognizes it as a new subtype in 2000 [1], there has always been a debate on subtypes of MBCs. It is a rare type of breast cancer, so that there are few cases and few studies on this topic. Lee et al. presented that squamous and spindle cell differentiations were associated with poorer survivals than other types of MBCs [23]. Cimino-Mathews and colleagues also demonstrated that there was no OS and LRFS difference between mixed subtypes and nonmixed subtypes of MBCs, but distant metastasis-free survival was significantly worse for mixed subtypes [24]. A multi-institutional study found that matrix-producing carcinomas presented better survival than spindle, squamous, and mixed histologic subtypes in a series of 283 patients [4]. The most recent and detailed analysis about survival of different subtypes of MBCs was presented by Tadros et al. [10]. They analyzed 132 MBC patients which 45 were heterologous mesenchymal (34.1%), 26 were squamous (19.7%), 26 were spindle (19.7%), and 30 were mixed (22.7%) subtype. They found that squamous subtype had the worse OS (50%; 95% CI: 26–73%) and DSS (56%; 95% CI: 32–79%). Heterologous mesenchymal subtype had the best OS (76%; 95% CI: 68–84%) and DSS (79%; 95% CI: 71–87%). In our series of 118 MBCs, we identified 93 cases with known subtype. They were stratified as 45 (48.4%) mesenchymal and 48 (51.6%) as other (squamous [n = 43], spindle [n = 3], and mixt [n = 2]). In Cox proportional hazard regression model, we found that mesenchymal subtype had the worse DFS (HR: 2.35; %95 CI: 1.01–5.48, p = 0.049) and DSS (HR: 3.16; %95 CI: 1.06–9.47, p = 0.040) than other subtypes. These results are different from published series by Tadros and colleagues [10]. Although we grouped squamous together with spindle and mixt subtype, most of the cases were squamous. Besides, the significant worse DFS and DSS of mesenchymal subtype did not change even after comparing solely mesenchymal and squamous subtypes. Another aspect of the discussion is the debate on how to classify subtypes of MBCs. It is first described

| Factors | 5-year DFS | 5-year DSS | 5-year LRFS |
|---------|------------|------------|-------------|
|         | HR (95% CI) | p value | % | HR (95% CI) | p value | % | HR (95% CI) | p value | % |
| Age     |            |          |    |            |          |    |            |          |    |
| <50     | 1.34 (0.60–2.98) | 0.475 | 73.8 | 1.85 (0.69–4.92) | 0.221 | 78.5 | 1.13 (0.23–5.60) | 0.882 | 93.9 |
| ≥50     | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| pT stage |            |          |    |            |          |    |            |          |    |
| I–II    | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| III–IV  | 3.19 (1.36–7.45) | 0.008* | 90.5 | 4.99 (1.95–12.75) | 0.001* | 93.3 | 1.29 (0.15–11.02) | 0.819 | 95.0 |
| pN stage |            |          |    |            |          |    |            |          |    |
| 0       | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| I–III   | 5.69 (2.36–13.69) | <0.001* | 90.6 | 16.34 (3.75–71.16) | <0.001* | 96.2 | 2.35 (0.47–11.81) | 0.300 | 95.1 |
| pStage  |            |          |    |            |          |    |            |          |    |
| I–IIA   | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| IIB–IIC | 4.89 (2.04–11.76) | <0.001* | 90.1 | 14.06 (3.23–61.23) | <0.001* | 96.0 | 2.01 (0.40–10.04) | 0.397 | 94.9 |
| Surgery type |           |          |    |            |          |    |            |          |    |
| BCS     | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| Mastectomy |          | 0.063 | 82.3 | 3.24 (1.25–8.42) | 0.16* | 89.3 | 1.01 (0.18–5.54) | 0.991 | 93.2 |
| NCT     |            |          |    |            |          |    |            |          |    |
| +       | 7.43 (2.97–18.58) | <0.001* | 50.5 | 6.56 (2.39–17.98) | <0.001* | 54.2 | 9.52 (1.59–57.06) | 0.014* | 83.3 |
| −       | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| LVI     |            |          |    |            |          |    |            |          |    |
| +       | 3.63 (1.59–8.23) | <0.001* | 58.8 | 6.78 (2.23–20.60) | <0.001* | 65.2 | 2.18 (0.44–10.82) | 0.343 | 91.7 |
| −       | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |
| Molecular subtype |       |          |    |            |          |    |            |          |    |
| TN      | 1.19 (0.28–5.05) | 0.816 | 76.0 | 2.37 (0.32–17.69) | 0.399 | 81.2 | Reference (1) | 0.079 | 95.3 |
| Nonluminal HER2 (+) |       |          |    | Reference (1) |          |    | Reference (1) |          |    |
| ≥70%    | 1.16 (0.43–3.12) | 0.766 | 82.9 | 1.29 (0.39–4.21) | 0.679 | 88.1 | Reference (1) | 0.672 | 95.6 |
| Metaplastic subtype |      |          |    |            |          |    |            |          |    |
| Mesenchymal |          | 0.092 | 69.3 | 1.91 (0.64–5.69) | 0.240 | 77.8 | 4.02 (0.45–36.16) | 0.214 | 91.6 |
| Other   | Reference (1) |          |    | Reference (1) |          |    | Reference (1) |          |    |

DFS, disease-free survival; DSS, disease-specific survival; LRFS, locoregional recurrence-free survival; HR, hazard ratio; CI, confidence interval; BCS, breast conserving surgery; NCT, neoadjuvant chemotherapy; LVI, lymphovascular invasion; HER2, human epidermal growth receptor-2. * p < 0.05; Cox regression analysis.
Worse Survival in Mesenchymal Metaplastic Cancers

in 2000, and there have been major changes on its sub-classification [1]. This means the classification of T subtypes in MBC may differ from institution to institution. As it is classified as heterologous mesenchymal in previous study [10], we classified it as purely mesenchymal. There are some limitations of the present study. First, this is a retrospective analysis and it has small number of cases. However, it is still one of the largest series about subtypes of MBCs in the literature. Another limitation is the classification of MBC subtypes. As mentioned before, there is still a debate on how to classify MBCs [10]. Basically, it is classified as mesenchymal or epithelial; we aim to compare mesenchymal subtype with other subtypes. Another issue which should be noted is that even mesenchymal subtype has significantly worse 5-year DFS ($p = 0.049$) and DSS ($p = 0.040$), and these $p$ values are significant at borderline. These values need to be interpreted cautiously, and only a study of much larger cases could resolve the discrepancy between the current study and the published study by Tadros et al. [10].

**Conclusion**

In summary, this study is one of the few studies about the survival outcomes of subtypes of MBCs. Nonetheless, it is the only study demonstrating that mesenchymal subtype had the worse survival outcomes. Since there are still controversial findings between our study and recently published study [10], a unified pathologic classification and further studies are needed to determine the outcome of different subtypes of MBCs in larger series.

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**Statement of Ethics**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is an observational study. The Istanbul University Istanbul Faculty of Medicine Research Ethics Committee has confirmed that no ethical approval is required for this retrospective study, and the study has been granted an exemption from requiring written informed consent.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Table 4. Cox proportional hazard regression model assessing factors associated with DFS and DSS**

| Factors       | DFS HR (95% CI) | p value | DSS HR (95% CI) | p value |
|---------------|-----------------|---------|-----------------|---------|
| Age           |                 |         |                 |         |
| <50           | 1.49 (0.65–3.41)| 0.343   | 2.44 (0.87–6.88)| 0.091   |
| ≥50           | Reference (1)   |         | Reference (1)   |         |
| pT stage      |                 |         |                 |         |
| I–II          | Reference (1)   | 0.024   | Reference (1)   | 0.002   |
| III–IV        | 3.0 (1.16–7.79) |         | 5.92 (1.89–18.57)|        |
| pN stage      |                 |         |                 |         |
| N0            | Reference (1)   | 0.002   | Reference (1)   | 0.001   |
| N1–3          | 5.01 (1.76–14.21)|        | 15.30 (3.03–77.36)|       |
| LVI           |                 |         |                 |         |
| –             | Reference (1)   | 0.670   | Reference (1)   | 0.719   |
| +             | 1.24 (0.46–3.39)|         | 1.26 (0.36–4.43)|         |
| Metaplastic subtype |             |         |                 |         |
| Mesenchymal   | 2.35 (1.01–5.48)| 0.049   | 3.16 (1.06–9.47)| 0.040   |
| Other         | Reference (1)   |         | Reference (1)   |         |

Hazard ratio (HR) is presented with their 95% confidence interval (CI) and the $p$ value. Cox regression analysis ($Method = Enter$). DFS, disease-free survival; DSS, disease-specific survival; LVI, lymphovascular invasion.
Author Contributions

All authors contributed to the study conception and design. Study concepts were designed by Enver Özkurt, Selman Emiroğlu, Neslihan Cabioğlu, Hasan Karanlık, Semen Önder, Mustafa Tükemen, Abdullah İğci, Vahit Özmen, and Mahmut Müslümanoğlu; data acquisition by Enver Özkurt and Selman Emiroğlu; quality control of data and algorithms by Enver Özkurt, Neslihan Cabioğlu, Hasan Karanlık, Semen Önder, Mustafa Tükemen, Abdullah İğci, Vahit Özmen, and Mahmut Müslümanoğlu; data analysis and interpretation by Enver Özkurt, Neslihan Cabioğlu, and Mahmut Müslümanoğlu; statistical analysis by Enver Özkurt; manuscript preparation by Enver Özkurt and Selman Emiroğlu; manuscript editing by Enver Özkurt, Neslihan Cabioğlu, and Mahmut Müslümanoğlu; manuscript review by Enver Özkurt, Neslihan Cabioğlu, Hasan Karanlık, Mustafa Tükemen, Abdullah İğci, Vahit Özmen, and Mahmut Müslümanoğlu. All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to confidentiality policies of the hospital but are available from the corresponding author on reasonable request.

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