Original Article

Investigation of Clinical and Histopathological Features in Invasive Lobular Breast Cancers

Memede Lobüler Kanserlerin Klinik ve Histopatolojik Özelliklerinin İncelenmesi

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ABSTRACT

Introduction: Analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.
Methods: Our study was conducted retrospectively. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions.
Results: Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients.
Discussion and Conclusion: Although invasive lobular carcinoma has histopathologically bilateral and multicentric features, it is a disease that can be treated surgically not only with mastectomy but also with breast-conserving surgery, similar to invasive lobular carcinomas.

Keywords: Lobular carcinoma, immunohistopathological feature, mastectomy, breast conserving surgery

ÖZET

Giriş ve Amaç: Meme kanserinin en sık görülen alt tiplerinden biri olan lobüler meme kanserlerinin; tanı, tedavi ve takip açısından önem taşıyacak, klinik ve immünohistopatolojik özelliklerini analiz etmektir.
Yöntem ve Gereçler: Araştırma retrospektif olarak yapılmıştır. Ocak 2019 – Ağustos 2022 tarihleri arasında meme kanseri tanısı alan ve tedavisi yapılan hastalar çalışmaya dahil edilmiştir.
Bulgular: Çalışmaya dahil edilen hastaların yaşları 28-81 (yıl) aralığında olup medyan yaş 53,04'tü. Hastaların 26'sı (%35,6) premenapozal iken 47'si (%64,4) postmenapozaldır. Unilateral özellikteki hasta sayısı 71'dir (%97.3). Bilateral invaziv lobüler karsinomlu hasta sayısı 2'dir (%2,7). 38 hasta ile en sık üst dış kadran lokalizasyonunda tümörlü hasta bulunmaktadır (%44,3). Üst dış kadranı sırası 11 hasta alt dış kadran ve 8 hasta ile santral lokalizyon da tümörlü hastalar takip etmektedir (%15,1 ve %11). Hastaların 42'sine (%57,5) meme koruyucu cerrahi, 31'ine (%42)mastektomi uygulandı.

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Hastaların 51'ine (%69,9) sentinal lenf nodu biyopsisi uygulandı. Aksiller diseksiyon uygulanan hasta sayısı 22'dir (%30,1).
Tartışma ve Sonuç: İnvaziv lobüler karsinom histopatolojik olarak bilateral ve multisentrik özelliklere sahip olsa da cerrahi olarak invaziv lobüler karsinomlar ile benzer şekilde sadece mastektomi değil meme koruyucu cerrahiyle de tedavi edilebilen bir hastalıktır

Anahtar Kelimeler: Lobüler karsinom, immünohistopatolojik özellik, mastektomi, meme koruyucu cerrahi

Introduction

Breast cancer is the most common cancer among women. It is the second most important cause of death due to cancer in women after lung cancer [1]. The incidence of breast cancer has increased in recent decades, especially in the younger age group. Despite the increase in the incidence and improvements in the treatment modalities of breast cancer, which is diagnosed early due to the developments in all screening and imaging methods, the mortality rate of the disease continues to be important and frightening. Conventional treatment methods for breast cancer include surgery, chemotherapy, radiotherapy and hormone therapy. Despite the developments in all treatment methods, especially chemotherapy, the need for new treatment modalities has increased due to the inability to achieve the expected survival rates in some subgroups. Patients with breast cancer have different prognoses after diagnosis, and there are differences in the disease biology in terms of progression and metastasis pathways; therefore, breast cancer has been classified, and different morphological variants have been defined. The final tumor classification of the WHO published in 2019 includes many variants of breast cancer, including a total of 44 major types and minor subtypes [2]. Nevertheless, some concerns have been raised about the biological significance of the identified variants. Despite the fact that many variants have been defined, they have not yet led to any changes in the clinical diagnosis, treatment, or follow-up practices of the disease.

Breast cancer is a heterogeneous disease. Invasive breast cancers are currently classified as the no special type of ductal carcinoma and special subtypes. Breast cancers of special subtypes have specific definitions, while the no special type is a general definition that includes carcinomas other than special subtypes. Non-specific type invasive ductal carcinomas (IDC) constitute approximately 60-75% of all breast cancers. Special subtypes account for 20-25% of all tumors and metaplastic, lobular, tubular, papillary, and mucinous tumors represent the most common types within this group [3, 4]. The histopathological features should be revealed effectively and in detail, and pathologic indicators concerning good and bad prognoses should be reviewed to treat patients with breast cancer under optimal conditions [5, 6].

Invasive lobular carcinomas (ILC) account for 15% of all breast cancers in women [7]. It is the most common group among special subtypes and has clinical and histo-pathological differences in terms of disease biology, with varied treatment and surgical options for the disease [8, 9]. The IDC usually emerges as a separate, palpable mass. In contrast, ILC is not well palpable and is often diagnosed late with multifocal, multicentric, or contralateral involvement [10]. Therefore, ILC develops differently, requiring different treatment modalities and prognoses [11].

In this study, we aimed to analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.

Materials and Methods

Our study was conducted retrospectively in the General Surgery-Surgical Oncology Clinic of the Gulhane Training and Research

Hospital of the University of Health Sciences. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions (Approval number E-50687469-199-210072112, Date 24.02.2023).

The demographic characteristics of patients with invasive lobular carcinoma were primarily recorded as age and menopausal status. The size and location of the disease at the time of diagnosis, its laterality, and the quadrants where the tumor was located were evaluated. The stage of cancer was determined by combining the type of surgery performed on the patients, the number of patients who had undergone sentinel lymph node biopsy and axillary dissection, the total number of lymph nodes removed in sentinel lymph node biopsy and axillary dissection, T(tumor size), N (metastatic lymph node count), and M (distant metastasis) results.

Tumor grades, immunohistochemical distribution of hormone profiles, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptors (HER2), and Ki67 proliferation index values of the patients were recorded. The status of surgical margins after surgery was examined. All data were recorded and analyzed using the SPSS 25.0 statistical software. Descriptive statistics were performed.

Results

Among the 728 patients diagnosed and treated in our clinic during the period specified, 73 had been diagnosed with ILC. Demographic, clinical, and pathological characteristics of patients with ILC were summarized in Table-1.

Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients. The number of lymph nodes removed in a sentinel lymph node biopsy was in the range of two and 12. The mean number of lymph nodes excised was 3.82 ± 1.42. The number of patients who had undergone axillary dissection was 22 (30.1%). The number of lymph nodes removed in axillary dissection was between eight and 25. The mean number of lymph nodes dissected was 14.82 ± 4.79. The distribution range for the number of metastatic lymph nodes was 1-5. The mean number was 2.86 ± 1.39.

Histologically, 62 (84.9%) of the patients with ILC had isolated lobular carcinoma, while 11 (15.1%) had mixed lobular carcinoma. Among the patients, 73 (100%) had ER, 67 (91.8%) had positive PR, and all had negative HER2. Ki-67 was evaluated in 67 of the patients. The distribution range for Ki-67 was 1.0-80.0 and the median Ki-67 proliferation index value was 20%. The tumor sizes were observed below 2 cm (T1) in 47.9%, between 2 and 5cm (T2) in 42.5%, and above 5 cm (T3) in 9.6% of the patients. In pathological staging, the number of patients without lymph node metastasis (N0) was 46 (63%), the number of patients with lymph node metastasis between 1 and 3 (N1) was 17 (23.3%), and the number of patients with lymph node metastasis between 4 and 9 (N2) was 10 (13.7%). There were 3 patients with histological grade 1 (4.1%), 65 patients with histological grade 2 (89%), and five patients with histological grade 3 (6.8%).

In invasive breast carcinoma, the membranous positivity of E-cadherin immuno-histochemically is typical in NST. Tumor cells with cytological loss of cohesion, generally forming scattered or "single file" aligned linear cords in a fibrous stroma or concentric placement around normal ducts,

Table 1. Demographic and Clinico-pathological Characteristics of the Patients

Age, years, mean ± SD, distribution	53,04±11,68 (28-81)
Side, n(%)	
Right	34 (%46,6)
Left	37 (%50,7)
Bilateral	2 (%2,7)
Tumor Localization, n(%)	
UOQ	38 (%44,3)
UİQ	6 (%55,6)
LOQ	11 (%15,1)
LİQ	5 (%6,8)
Central	8 (%11)
UOQ+Central	3 (%4,1)
Multifocal	2 (%2,7)
Tumor Type, n(%)	
İsolated Lobular Carcinoma	62 (%84,9)
Mixed Lobular Carcinoma	11 (%15,1)
Operation, n(%)	
Breast Conserving Surgery	42 (%57,5)
Mastectomy	31 (%42,5)
Axillary İnterference, n(%)	
SLNB	51 (%69,9)
ALND	22 (%30,1)
SLNB Lymph Node Dissection, number, mean±SD, distribution	3,82±1,42 (2-12)
ALND Lymph Node Dissection, number, mean±SD, distribution	14,82±4,79 (8-25)
ALND Lymph Node metastasis, number, mean±SD, distribution	2,86±1,39 (1-5)
N Stage, n(%)	
N0	46 (%63)
N1	17 (%23,3)
N2	10 (%13,7)
T Stage, n(%)	
T1	35 (%47,9)
T2	31 (%42,5)
T3	7 (%9,6)
Ki 67,percent, mean±SD, distribution	16,86±14,92 (1-70)
Nottingham grade, number, mean±SD, distribution	6,51±0,71 (5-8)
Histological grade, number, mean±SD, distribution	
Grade 1	3 (%4,1)
Grade 2	65 (%89)
Grade 3	5 (%6,8)
Menopause Status, n(%)	
Premenopausal	26 (%35,6)
Postmenopausal	47 (%64,4)

UOQ: Upper Outer Quadrant UİQ: Upper İnner Quadrant LOQ: Lower Outer Quadrant LİQ: Lower İnner Quadrant SLNB: Sentinel lymph node biopsy ALND: Axillary lymph node dissection

are common in ILC (Figure 1 and 2). The tumor consists of uniform cells with round or ovoid nuclei, narrow cytoplasm, low mitotic activity, and usually mild pleomorphism. Intracytoplasmic lumen formations or central mucoid inclusions can be observed in neoplastic cells. In ILC, the loss of E-cadherin protein causes a discohesive appearance in cells. Therefore, immunohistochemical loss of E-cadherin expression is observed in approximately 85% of cases. Nevertheless, E-cadherin expression can be observed in approximately 15% of the cases. In such cases, it is recommended to refer to the morphology (Figure 3).

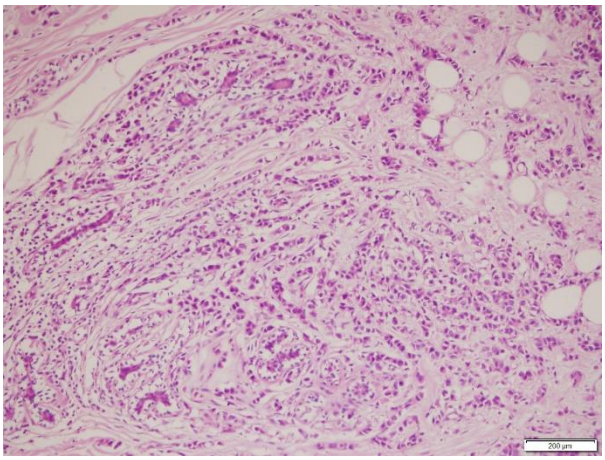

Figure 1. invasive lobular carcinoma, classical type

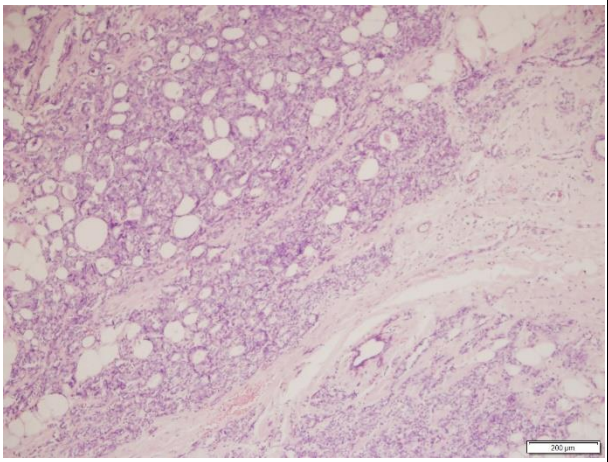

Figure 2. invasive breast carcinoma,NST

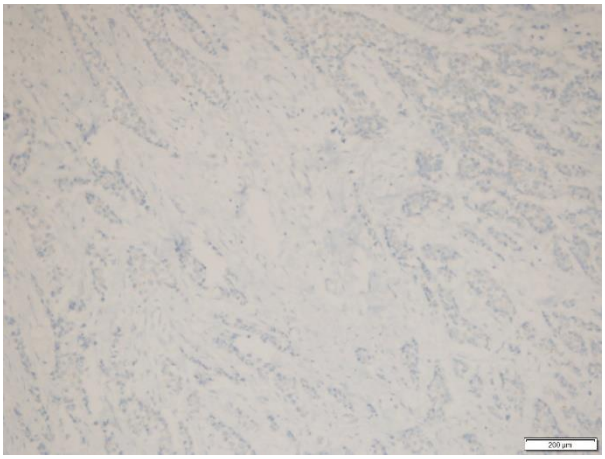

Figure 3: Immunohistochemical loss of e-cadherin in invasive lobular carcinoma

Discussion

Invasive lobular carcinoma is the second most common type of invasive breast cancer after IDC. ILC has unique clinical, pathological, and radiographic features, suggesting a separate clinical entity; however, it is treated with the same treatment paradigms as IDC. There is limited information about the specific treatment of ILC, including the response to standard therapy. In this study, 10.2% of the patients treated for breast cancer were determined to be of the ILC histological type, and this rate was found to be consistent with the literature.

Generally, women with ILC are slightly older compared to women with ICD at the time of diagnosis. The mean age of 53.04 was found to be compatible with the public health cancer statistics data of Turkey and the study conducted by Ozmen V (mean age 51.6) [12]. In the study of Enrico Orvieto et al., 36.8% of the patients were premenopausal and 63.2% were postmenopausal. Similar to the literature, 35.6% were premenopausal and 64.4% were postmenopausal in our study [13, 14].

ILC generally involves normal tissues without the intense desmoplastic response that usually accompanies IDC. The mass in the breast is not always a pronounced clinical feature, and sometimes it is difficult to distinguish it from the dense normal breast parenchyma. More than one-third is determined by asymmetric density, poorly defined opacity, and structural distortion in mammography. Microcal-cifications screened on mammography are common symptoms of ductal carcinomas and are rarely detected in ILC. In ultrasonography (USG), the ILC appears as a heterogeneous hypoechoic mass with irregular margins and a posterior acoustic shadow. Some studies have demonstrated that USG has a higher sensitivity compared to mammography in detecting ILC and has the advantage of evaluating the presence of axillary lymph node metastasis. On the other hand, sensitivity in detecting ILC varies in the studies between 57-81% for mammography and 68-87% for

USG [15]. In the diagnosis of ILC and ICD, digital breast tomosynthesis and contrast-enhanced digital mammography are more sensitive compared to standard mammography [16, 17, 18]. USG is preferred as a complementary imaging method to standard mammography [19]. Greater multifocality and multicentricity in ILC is one of the factors causing the decrease in sensitivity in standard mammography compared to ICD. For all these reasons, breast magnetic resonance imaging (MRI) is recommended for all patients with ILC, unlike ICD. USG and breast MRI are recommended for both pre-operative evaluation and postoperative follow-up [19, 20].

Whether the prognosis in the ILC of the breast is different from the IDC is still a matter of discussion. Despite the controversy, factors affecting prognosis and treatment protocols are generally similar for both histological types. Nevertheless, ILC has been reported to be more frequently associated with factors such as advanced age at the time of diagnosis, large tumor size, multicentricity, multifocality, bilateralism, hormone receptor positivity, and HER2 negativity [11, 15].

ILC is almost always ER-positive and PR-positive. Excessive expression and/or amplification of HER2 is rare (3-13%). However, HER2 overexpression and/or amplification develop in a subset of pleomorphic ILCs. While 90-95% of patients with ILC have luminal A, this rate is 50% in ICD. Six studies analyzed ER, PR, and HER2 in detail and found that ICD was associated with triple-negative and HER2 with molecular subtypes, while ICL was associated with the luminal A subgroup. In this study, the ER receptor was positive in all patients, while 67 (91.8%) were PR positive and all were Cerb-B2 negative. These rates were consistent with the literature.

In terms of the location of the disease, ILC is more often multifocal. ILC is considered to have higher rates of bilateral disease; however, Pestalozzi et al. calculated similar rates of bilateral disease for IDC and ILC [22]. In our study, only two (2.7%) of the patients were bilateral.

Some studies in the literature observed the highest tumor size frequency in the T1 stage compared to the American Joint Committee on Cancer (AJCC) TNM staging criteria, while some studies observed it more frequently in the T2 stage. The percentage of T1 patients was found to be higher in our study, [21, 23, 24, 25, 26, 27]. In the literature, N0 has been demonstrated as the most common stage in terms of lymph node involvement, and it was followed by N1, N2, and N3, respectively. Pathological lymphatic stages were defined as pN0 by 50%, pN1 by 28%, pN2 by 15%, and pN3 by 7% [23, 24]. In our study, the lymph node status was pN0 by 63%, pN1 by 23.3%, and pN2 by 13.7%. In terms of distant metastasis, metastasis to bone and liver is frequent in both ILC and ICD. Unlike in ILC, the areas with greater metastatic spread are the abdominal cavity and the leptomeninges. Metastasis to the lung and central nervous system is less common compared to ICD [28, 29, 30, 31].

The general surgical treatment approach for breast cancer includes breast-conserving surgery (BCS) or mastectomy and systemic treatment depending on tumor characteristics such as tumor size, grade, lymph node, hormonal, and growth receptor status. One of the important points for the surgical treatment of invasive lobular cancer is the ability to choose the appropriate method among the BCS or mastectomy options due to the high rates of multifocality, multicentricity, and bilaterality. Fodor et al. investigated the long-term outcomes of BCS and mastectomy in ILC. For 15 years, they observed 235 patients with early-stage ILC who were prospectively treated with mastectomy or BCS. They found similar results for mastectomy and BCS in 15 years. Distant metastatic-free survival (62% vs. 70%; P= .2017), breast cancer-specific survival (62% vs. 70%; P= .1728), and regional recurrence-free survival (84% vs. 77%); P= .0644). Interestingly, better overall survival (OS) was observed in the BCS group compared to the mastectomy group (63% vs.

49% P= .0122) [32]. The fact that ILC is more multifocal and multicentric compared to IDC does not imply any contraindications for BCS. According to our patient data, 57.5% of the patients had undergone BCS, while 42.5% had undergone mastectomy. Our standard treatment policy is not based on the type of tumor histology. In their study, Biglia et al. concluded that a second surgery (conservative rejection/mastectomy) was necessary for a significantly higher percentage of patients with ILC to achieve negative limits. In general, there was no difference in the total number of mastectomies performed for ILC and IDC. In the multivariate analysis, only multifocality and tumor size (not histological type, grading, age, ER, and HER-2 status) were found to be independent predictors for re-excision or doubling the risk. In the first surgical approach, no significant difference was observed between the IDC and ILC groups, and BCS was the preferred treatment for most patients [21]. Recent studies have reported mastectomy rates ranging from 22% to 52% in patients with ILC (compared to 14% to 46% in patients with ICD). A positive surgical margin rate between 17% and 65% has been reported in patients with ILC undergoing BCS [33]. Similar to ICD, no improvement was observed in patients with ILC in terms of long-term survival after mastectomy compared to BCS with clear margins and the combination of radiotherapy [34].

Compared to the patients with ICD, patients with ILC appear to benefit less from neoadjuvant chemotherapy (NACT) administered to facilitate BCS and shrink the tumor. Low proliferation rate and high ER expression make ILC less susceptible to chemotherapy, as reflected by low pathological complete response (pCR) rates [36, 36, 37, 38]. There are conflicting results as to whether these low pCR rates can be attributed to differences in ER expression. Lips et al. found no difference between patients with ICD and ILC in response to chemotherapy [39]. Nevertheless, other studies have shown that the rate of pCR is still lower in patients with ILC when comparing ILC and ICD with a similar receptor status [40]. Although pCR appears to be a good prognostic factor for most breast cancers, this may not be the case for ILC, as low pCR rates do not lead to significantly worse outcomes in patients with ILC compared to ICD. Most patients with ILC still require mastectomy after NACT due to the lack of response to NACT [37, 41, 42].

Several studies have reported a higher nodal stage at diagnosis and a higher number of positive lymph nodes during surgery in ILC compared to ICD, leading to a higher rate of axillary lymph node dissection [22, 43, 44]. Since this is no longer seen in multivariate analysis, it can be attributed to larger tumor sizes and other misleading factors [45]. After sentinel lymph node biopsy, there is a 38% nodal positivity rate in node-negative patients, which highlights the challenges of clinical nodal evaluation in ILC [46].

Although ILC accounts for only a small percentage of invasive cancers, the pathogenesis, diagnosis, and clinical course of ILC have unique aspects and deserve special attention. Current analyses have demonstrated that the histology of ILC provides less benefit compared to NACT and tumors with ductal morphology. Despite the challenges in terms of radiological diagnosis and localization, BCS is preferred as an important treatment option for ILCs. While research on breast cancer is quite extensive, research on ILC is more limited. Further research is needed in this area, including providing an overview of ILC and treatment considerations that focus on early-stage treatment, particularly in the neoadjuvant setting.

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