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The potency of multiple synchronous ipsilateral tumours on quantity of axillary lymph node involvement in clinical early stage breast cancer

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Abstract

Aim: The purpose of this study was to compare multiple synchronous ipsilateral breast cancer (MSIBC) with unifocal breast cancer (UBC) in terms of the quantity of axillary lymph node involvement (ALNI) and to examine the factors that increase the number of ALNI in MSIBC.

Materials and Methods: Patients who were diagnosed with clinical early-stage breast cancer (stage I, II) with cN0 were included in the study.

Results: Patients were divided into two groups according to multifocality (MSIBC, n=142, 26.2%; UBC, n=400, 73.8%). Statistically significant differences in ALNI were found between the two groups ($p < 0.001$). Patients with MSIBC had significantly higher number of total positive lymph nodes, involvement of three or more axillary lymph nodes, tumor size, intermediate-high grade tumor, microcalcification, lymphovascular invasion (LVI), and accompanying ductal carcinoma in situ (DCIS) than patients with UBC ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.041$, $p < 0.001$, $p < 0.001$, $p = 0.035$, respectively). Out of the 142 patients who had MSIBC, 107 (75.4%) had ≤ 2 ALNI and 35 (24.6%) had > 2 ALNI. Presence of pT2 tumor, grade 2/3 tumor, C-erbB2 positivity, microcalcification, and LVI for MSIBC patients with > 2 ALNI were significantly higher than patients with ≤ 2 ALNI ($p = 0.003$, $p < 0.001$, $p = 0.048$, $p < 0.001$, $p = 0.002$, respectively). Presence of pT2 tumor, microcalcification, LVI, and grade 2/3 tumor were found to be significant after multivariate analysis for > 2 ALNI in MSIBC patients.

Conclusion: These results show that MSIBC not only increases ALNI in breast cancer patients, but also increases the number of involved lymph nodes. In MSIBC, limited axillary sampling can be performed more safely by identifying subgroup patients that may have increase number of ALNI.

Introduction

The incidence of multiple synchronous ipsilateral breast cancer (MSIBC) ranges from 9-77% [1-3]. MSIBC is defined as two or more separate tumors in the same breast [4]. Axillary nodal status is one of the important prognostic factors in early-stage breast cancer (BC) [5]. MSIBC has been reported to be associated with increased lymph node metastases (4). However, it is known that breast-conserving surgery in eligible MSIBC patients does not increase local recurrence as compared to a mastectomy [6]. The number of axillary lymph nodes involved in the management of early-stage breast cancer patients undergoing breast-conserving surgery is as important as whether there is axillary involvement or not. Complete axillary dissection can be safely omitted in eligible early-stage BC patients who have not received neoadjuvant therapy, have two or less sentinel lymph node (SLN) involvement, and are scheduled for radiotherapy [7]. The diagnostic reliability of SLN biopsy in MSIBC has been demonstrated [8]. However, it is controversial how reliable the above-mentioned procedure is to achieve regional control in early-stage MSIBC. It can be inferred that the quantitative load of axillary lymph node involvement (ALNI) may both change the treatment procedure and reflect a different biological behavior for MSIBC. So, the limited data on this issue prompted us to investigate the quantity of ALNI between unifocal breast cancer (UBC) and MSIBC.

The aim of this study was to compare MSIBC with UBC in terms of the quantity of ALNI and to examine the factors that increase the number of ALNI in MSIBC.

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Materials and Methods

The study was carried out retrospectively on the files of a total of 542 patients who were diagnosed with early-stage breast cancer with cN0, had no micrometastases or isolated tumor cells in SLN, had not received neoadjuvant therapy, and had complete data between January 2010 and December 2021 available in electronic files or paper files. Institutional Ethics Committee of Ankara City Hospital approved the study (ethics committee approval number: E1-2131) on March 22, 2021.

All patients were evaluated with a bilateral breast ultrasonography before surgery, and patients aged ≥ 40 years were evaluated with a bilateral mammography for BC diagnosis and treatment planning. The diagnosis of BC was made by tru-cut biopsy, stereotaxic biopsy, or excisional biopsy performed on the suspicious breast mass. All patients had SLN biopsy, and those with positive lymph nodes underwent axillary lymph node dissection. All the SLN biopsy procedures were conducted via the use of blue dye such as patent blue, isosulfan blue and methylene blue. All identified blue nodes were accepted as SLNs and harvested. Pathologic evaluation of SLNs was performed with frozen section analysis intraoperatively, which included sectioning at 2 mm intervals and staining with hematoxylin and eosin (H&E). Patients and tumor characteristics, such as age, pathological size of the tumor (pT), pathological lymph node status (pN), estrogen receptor (ER), progesterone receptor (PR), HER2-neu receptor, nuclear grade, lymphovascular invasion (LVI), histological type, total number of SLNs removed, total number of ALNI, mammographic microcalcification, and, tumor multiplicity were collected retrospectively. The largest tumor diameter in MSIBC was used as tumor size in data. Favorable histologic-type tumors are defined as pure tubular, pure mucinous, pure cribriform, encapsulated or solid papillary thyroid carcinoma, and adenoid cystic carcinoma. In MSIBC, tumors having different histopathological types in the same breast were named as mixed tumors and were added to the class others.

The patients were divided into two groups as UBC and MSIBC. MSIBC was defined as multicentric and multifocal tumors diagnosed in the same breast at the same time. Multifocal and multicentric tumors were defined as tumors located in the same quadrant and different quadrants in the ipsilateral breast, respectively. Afterwards, the relationship between multiplicity of tumor and ALNI was investigated statistically.

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of data distribution. All continuous data were skewed. For continuous variables, median (IQR: Interquartile Range) was demonstrated. Differences in continuous variables in two groups were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using Chi-square (X^2) or Fisher's exact test. Crosstab was created for the relationship between categorical variables and Spearman correlation coefficient was calculated. Variables associated with three or more ALNI in patients with MSIBC were analyzed by logistic regression (with enter method). In logistic regression, $p \leq 0.05$ for entry to the model and $p \geq 0.10$ for removal from the model were taken as the limit. Logistic regression results were given as Exp(B) (OR), 95% CI of OR, and p value. Data were analyzed at 95% confidence level and p value less than 0.05 was considered to be significant. IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis.

Results

A total of 542 female patients with a median age of 53.0 years (IQR=17.0, range from 21 to 96) were included in this study. A total of 400 (73.8%) patients in UBC group and 142 (26.2%) patients in MSIBC group were analyzed. The histological types of tumors were invasive ductal carcinoma in 415 (76.6%), invasive lobular carcinoma in 22 (4.1%), favorable breast carcinoma in 56 (10.3%), and others (mixed tumors, micropapillary, apocrine differentiation, medullary pattern ductal carcinoma, metaplastic carcinoma) in 49 (9.0%) patients. There was no significant difference between groups in terms of histological types.

The median pathological tumor size was 20.0 mm (IQR=12.0, range 1-50 mm). A total of 308 (56.8%) patients had a pT1 tumor while 234 (43.2%) patients had pT2 tumor. Statistically significant differences in pathological tumor sizes were found between the two groups ($Z = 19.998$, $p < 0.001$).

Total ALNI rate was 40.8% (n=221) and number of ALNI median value was 0.0 (IQR=1.0, range 0 - 47). pN0 in 315 (58.1%), pN1 in 172 (31.7%), pN2 in 37 (6.8%) and pN3 in 18 (3.3%) were detected in all breast cancer patients.

Presence of DCIS accompanying invasive cancer was histologically detected in 338 (62.4%), patients and presence of DCIS accompanying invasive cancer had statistically significant correlation with multifocality ($Rho = 0.090$, $p = 0.035$).

The comparison of all clinicopathological data between the groups is shown in Table 1 and 2. In order to find the clinical and pathological features that affect the number of ALNI in MSIBC, this group was divided into two groups as follows: those with ≤ 2 ALNI and > 2 ALNI. The comparison of the characteristics of MSIBC with and without involvement of three or more axillary lymph nodes is shown in Table 3. Out of the 142 patients who had MSIBC, 107 (75.4%) had ≤ 2 ALNI and 35 (24.6%) had > 2 ALNI. Presence of pT2 tumor, grade 2/3 tumor, Cerb B2 positivity, microcalcification, and LVI for MSIBC patients with > 2 ALNI was significantly higher than patients with ≤ 2 ALNI (Table 3). Multivariate analysis revealed that pT2 tumor, microcalcification, LVI, and grade 2/ 3 tumor were associated with >2 ALNI independent of other parameters in patients with MSIBC (-2LL=119.279, Nagelkerke $R^2 = 0.360$) (Table 4).

Discussion

ALNI is the strongest prognostic factor in early-stage breast cancer [5]. Currently, beyond axillary assessment for staging, axillary management procedures in breast cancer for regional control have changed. Minimal axillary intervention is recommended to reduce the complication rate due to axillary dissection in regional control for early-stage breast cancer, after the SLN biopsy was used for

Table 1. Demographic characteristic of clinical early-stage breast cancer patients.

Clinical and pathological variables	UBC n=400 (73.8%)	MSIBC n=142 (26.2%)	Test Statistics	p
Age ,median (IQR) (years)	53.0 (16.0)	52.0 (18.0)	Z=1.095	0.273
Tumor size, median (IQR) (mm)	20.0 (13.0)	20.5 (15.0)	Z=19.998	<0.001
Microcalcification (n,%)				
Absent	282 (70.5%)	64 (45.1%)	X^2=29.356	<0.001
Present	118 (29.5%)	78 (54.9%)		
Accompanying DCIS (n,%)				
Absent	161 (40.3%)	43 (30.3%)	X^2=4.437	0.035
Present	239 (59.7%)	99 (69.7%)		
pT (n,%)				
pT1	237 (59.2%)	71 (50.0%)	X^2=29.356	<0.001
pT2	163 (40.8%)	71 (50.0%)		
pN (n,%)				
pN0	265 (66.2%)	50 (35.2%)	X^2=47.523	<0.001
pN1	108 (27.0%)	64 (45.1%)		
pN2	16 (4.0%)	21 (14.8%)		
pN3	11 (2.8%)	7 (4.9%)		
Histological grade (n,%)				
Grade I	116 (29.0%)	33 (23.2%)	X^2=6.388	0.041
Grade II	179 (44.7%)	81 (57.0%)		
Grade III	11 (26.3%)	7 (19.7%)		
ER (n,%)				
Negative	81 (20.3%)	28 (19.7%)	X^2=0.018	0.892
Positive	319 (79.7%)	114 (80.3%)		
PR (n,%)				
Negative	81 (20.3%)	26 (24.3%)	X^2=0.249	0.618
Positive	319 (79.7%)	116 (26.7%)		
Cerb B2 (n,%)				
Negative	319 (79.7%)	107 (75.4%)	X^2=1.205	0.272
Positive	81 (20.3%)	35 (24.6%)		
Triple negative (n,%)				
Absent	355 (88.7%)	133 (93.7%)	X^2=2.819	0.093
Present	45 (11.3%)	9 (6.3%)		
LVI				
Absent	295 (73.7%)	64 (45.1%)	X^2=38.543	<0.001
Present	118 (26.3%)	78 (54.9%)		
Histopathological diagnosis				
IDC	305 (76.2%)	110 (77.5%)	X^2=4.036	0.258
ILC	18 (4.5%)	4 (2.8%)		
Favorable type	37 (9.3%)	19 (13.4%)		
Others	40 (10.0%)	9 (6.3%)		

*DCIS: Ductal carcinoma in situ, ER: The estrogen receptor, PR: Progesterone receptor $\geq$ 1% were considered positive, LVI: Lymphovascular Invasion, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, UBC: Unifocal breast cancer, MSIBC: Multiple synchronous ipsilateral breast cancer.

routine staging and the Z011 procedure was standardized for axillary management in eligible breast cancer patients [9]. Thus, the number of axillary lymph node involvement has gained importance for surgical management. However, axillary dissection is still recommended for breast cancer patients with three or more involvements in SLN sampling, even if other conditions are suitable to omit axillary surgery [10]. It is also known that axillary involve-

Table 2. Relationship between axillary lymph node involvement and multicity of tumor in clinical early-stage breast cancer.

Clinical and pathological variables	UBC*	MSIBC**	Test Statistics	p
Number of total positive lymph nodes ,median (IQR)	0.0 (1.0)	1.0 (2.3)	Z=6.691	<0.001
ALNI ,n (%)				
Absent	271 (67.7%)	50 (35.2%)	X^2=45.946	<0.001
Present	129 (32.3%)	92 (64.8%)		
ALNI according to Pt1 ,n (%)				
Absent	180 (15.9%)	36 (50.7%)	X^2=16.622	<0.001
Present	57 (24.1%)	35 (49.3%)		
ALNI according to Pt2 ,n (%)				
Absent	91 (55.8%)	14 (19.7%)	X^2=26.070	<0.001
Present	72 (44.2%)	57 (80.3%)		
ALNI Categories ,n (%)				
≤2 lymph node involvement	360 (90.0%)	107 (75.4%)	X^2=18.859	<0.001
>2 lymph node involvement	40 (10.0%)	35 (24.6%)		

*UBC: Unifocal breast cancer, MSIBC: Multiple synchronous ipsilateral breast cancers.

ment is more common in multifocal/multicentric breast cancer than in UBC [11,12]. More frequent ALNI in multifocal/multicentric breast cancer may be due to higher tumor burden or aggressive behavior of the tumor. Cabioglu et al. showed that increased total tumor diameter, especially in T2 tumors, is associated with increased ALNI [4]. In our study, the tumor size was evaluated according to the largest tumor diameter in MSIBC. In our patient series, largest tumor diameter was found to be higher in MSIBC compared to tumor diameter in UBC. However, there is no significant difference between the distribution of MSIBC and UBC when we compare them in terms of pT. Similar to Cabıoglu et al.'s study, when pT1 and pT2 tumors are evaluated separately in terms of axillary involvement, ALNI is high in MSIBC in both tumor stages [4]. In this case, the increased ALNI in MSIBC can also be attributed to the aggressive behavior of the tumor. MSIBC can be correlated with clinical and pathological factors suggestive of aggressive biology, such as young age, higher grade, ER or PR status, HER-2 status, and LVI [11]. Consistent with this view, high-intermediate grade and LVI were observed significantly more frequently in MSIBC than in UBC in our study. In studies examining the behavior of multifocal/multicentric breast cancer, it was stated that LVI was detected more frequently in MSIBC patients [11,12]. On the other hand, different results in the literature exist for high grade pattern accompanying multifocality [4,11-15].

Various conditions have been described for the development of multiple invasion foci in breast cancers such as extensive carcinoma in situ with multiple foci, invasive carcinoma with satellite foci, invasive carcinoma with LVI, multiple biologically distinct invasive carcinomas, multiple residual foci after neoadjuvant therapy, and segmentation of a single carcinoma into multiple fragments [16]. Considering the role that carcinoma in situ of multiple foci may play in the etiopathogenesis of multifocal/multicentric breast cancer, it can be explained why DCIS borderly significantly more frequent accompaniment in MSIBC in our study.

In our study, it was shown that ALNI was significantly higher in MSIBC than in UBC, which was consistent with the literature [11-13,17]. Moreover, we found that the number of axillary lymph nodes involved is also significantly higher in MSIBC, which may affect axillary management. It is stated that breast-conserving surgery can be applied in suitable patients with MSIBC tumors [15]. SLN biopsy is also generally considered safe for axillary sampling in MSIBC patients [8,18]. However; Z011 does not clearly cover axillary management of MSIBC patients with SLN positive. Atas et al. found that the presence of MSIBC is an independent factor for nonsentinel lymph node involvement [19]. Due to the high level of axillary involvement in MSIBC patients, SLN positivity in these patients may lead to overtreatment for axillary management. Therefore, independent factors affecting $\geq$ 2 ALNI in MSIBC were also examined in this study.

The factors affecting ALNI in breast cancer are generally defined in the literature as age at diagnosis, tumor size, LVI, multifocality, radiologically reported suspicious lymph node, molecular subtype, and pathological type (17,20,21). The factors that may affect the ALNI burden in MSIBC tumors are not mentioned in the literature. In this study, presence of pT2, microcalcification, LVI, and histological grade 2-3 tumor were determined as independent factors affecting the involvement of three or more lymph nodes in the axilla in MSIBC. The patient group with the features mentioned in MSIBC, in which axillary involvement is more common, can be investigated more meticulously preoperatively and periperatively for axillary staging. The sensitivity in preoperative examination and estimation of the involved lymph node load in MSIBC may also affect the neoadjuvant treatment decision. In the perioperative examination, dual staining in order to obtain adequate SLN sampling and suspicious nonsentinel lymph

Table 3. Comparison of the characteristics of MSIBC with and without involvement of three or more axillary lymph nodes.

Clinical and pathological variables	ALNI ≤2 n=107 (75.4%)	ALNI >2 n=35 (24.6%)	Test Statistics	p
Age ,median (IQR)	53.0 (16.0)	49.0 (20.0)	Z=1.478	0.140
Tumor size (mm) ,median (IQR)	20.0 (12.0)	25.0 (15.0)	Z=3.093	0.002
Microcalcification (n,%)				
Absent	58 (90.6%)	6 (9.4%)	X^2=14.633	<0.001
Present	49 (62.8%)	29 (37.2%)		
Accompanying DCIS (n,%)				
Absent	37 (86.0%)	6 (14.0%)	X^2=3.798	0.051
Present	70 (70.7%)	29 (29.3%)		
pT (n,%)				
pT1	61 (85.9%)	10 (14.1%)	X^2=8.531	0.003
pT2	46 (64.8%)	25 (35.2%)		
Histological grade (n,%)				
I	32 (97.0%)	1 (3.0%)	X^2=10.817	<0.001
II-III	75 (68.8%)	34 (31.2%)		
ER (n,%)				
Negative	21 (75.0%)	7 (25.0%)	X^2=0.002	0.962
Positive	86 (75.4%)	28 (24.6%)		
PR (n,%)				
Negative	20 (76.9%)	6 (23.1%)	X^2=0.042	0.837
Positive	87 (75.0%)	29 (25.0%)		
Cerb B2 (n,%)				
Negative	85 (79.4%)	22 (20.6%)	X^2=3.095	0.048
Positive	22 (62.9%)	13 (37.1%)		
Triple negative (n,%)				
Absent	100 (75.2%)	33 (24.8%)	X^2=0.030	0.861
Present	7 (77.8%)	2 (22.2%)		
LVI				
Absent	56 (87.5%)	8 (12.5%)	X^2=9.258	0.002
Present	51 (65.4%)	27 (34.6%)		

* ALNI: Axillary lymph node involvement, DCIS: Ductal carcinoma in situ, ER: The estrogen receptor, PR: Progesterone receptor ≥ 1% were considered positive, LVI: Lymphovascular Invasion.

Table 4. Multivariate analysis of clinical and pathological characteristics associated with involvement of three or more axillary lymph node in MSIBC.

	Exp (B)	95% CI	p
Accompanying DCIS	2.193	0.748-6.434	0.153
pT2	3.308	1.305-8.386	0.012
Cerb B2 positivity	1.487	0.563-3.929	0.424
Presence of microcalcification	3.136	1.099-8.946	0.033
LVI	3.041	1.140-8.114	0.026
Histological grade II-III	8.855	1.078-72.724	0.042

*DCIS: Ductal carcinoma in situ, LVI: Lymphovascular Invasion, MSIBC: Multiple synchronous ipsilateral breast cancers.

nodes may need to be evaluated more carefully.

This study has several limitations. This study was carried on in a long period, so in some of the patients, the same specialized breast radiologist didn't examined all of the patients with ultrasonography. Therefore, there is significant proportion of node-positive patients who were not detected in the preoperative evaluation. The retrospective design may have limited the results in the analysis of some clinical variables. Another limitation may be the lack of tumor size homogenization for both groups, although the groups were homogeneous by pT. However, to our knowledge, it is the first study to report the potency of MSIBC in terms of the quantity of axillary lymph node involvement (ALNI). The presence and number of ALNI is higher in MSIBC than in UBC. SLN sampling is also recommended for MSIBC patients [18]. However, further management of the axilla

in MSIBC patients with SLN positive is not standardized. Because this study showed that axillary lymph node load is higher in patients with pT2, microcalcification, LVI, and histological grade 2/3 tumor in MSIBC patients, it may be beneficial to the clinician in the axillary management of these patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval

Institutional Ethics Committee of Ankara City Hospital approved the study (Ethics Committee approval number: E1-2131) on March 22, 2021.

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