JBUON 2016; 21(4): 851-858
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Left laterality is an independent prognostic factor for metastasis in N3 stage breast cancer

Fatih Karatas[1], Suleyman Sahin[1], Gokmen U. Erdem[2], Ozturk Ates[3], Taner Babacan[3], Serkan Akin[3], Ali R. Sever[4], Yavuz Ozisik[3], Kadri Altundag[3]

[1]Diskapi Education and Research Hospital, Department of Medical Oncology, Ankara; [2]Ankara Numune Training and Research Hospital, Ankara; [3]Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara; [4]Hacettepe University Cancer Institute, Department of Radiology, Ankara, Turkey

Summary

Purpose: *Development of metastasis in patients with breast cancer (BC) is the most important negative prognostic factor and this process mainly begins with lymphatic involvement. Therefore, axillary, subclavicular, internal mammary or supraclavicular nodal involvement is a crucial step before metastasis. Anatomical differences between the right and left lymphatic drainages of the breasts may significantly affect the rate, site and time to development of distant metastasis. The purpose of this study was to investigate if laterality is an independent prognostic factor for metastasis in N3 breast cancer patients.*

Methods: *From a total of 4215 BC patients diagnosed between 1994 and 2015 in our center, 305 non-metastatic women with pathological N3 (pN3) nodal status at presentation were enrolled in this study. Patients were divided into two groups: left and right BC. Analysis of overall survival (OS) and time to first metastasis (TTM) was performed according to Kaplan-Meier method with log-rank test.*

Results: *The median number of lymph node involvement and lymph node ratio (number of positive lymph nodes / total number of excised lymph nodes) between the two groups was equal (14 and 0,66 respectively). Recurrence was observed in 123 patients [53 (35%) right vs 70 (44%) left group]. Patients with left BC had significantly higher rate of axial bone metastases compared with the right BC group (55.7 vs 35.8%, p<0.02, respectively). TTM was significantly shorter in the left BC group [49.1 months (95% CI 36.5-61.8) vs 103.6 months (95% CI 47.0-160); p=0.03, respectively]. Median OS did not differ between the groups, however, there was a trend towards lower OS in patients with left BC (p=0.68).*

Conclusion: *Left laterality in patients with pN3 non-metastatic BC is an independent prognostic factor associated with shorter TTM, increased risk of distant metastases and axial bone involvement compared with right laterality.*

Key words: *breast cancer, laterality, N3, survival, time to first metastasis*

Introduction

In human anatomy, visceral, paired organs and lymphovascular structures are not symmetrical. The asymmetrical nature of the body leads to a right or left laterality which affects incidence and prognosis for many diseases. Such anatomical asymmetry in arterial, venous or lymphatic vessels may have an effect on the course of the diseases. For example, varicoceles are up to 80-90 times more common in the left testicle compared to the right due to the different drainage ways of left and right testicular veins [1]. There are several studies regarding the impact of laterality on survival, more importantly in esophageal and lung cancer [2,3]. Indeed in women with lung cancer,

Correspondence to: Kadri Altundag, MD. Hacettepe University Cancer Institute, Department of Medical Oncology 06100 Ankara, Turkey.
Tel: +90 312 3052939, Fax: +90 312 3242009, E-mail: altundag66@yahoo.com
Received: 01/01/2016; Accepted: 14/01/2016

left laterality was shown to have an adverse effect on survival [3].

The lymphatic flow of each breast drains into ipsilateral axillary lymph nodes. The right axillary lymph nodes drain into the right thoracic duct and then into the right subclavian vein via the right *angulus venosus*. Likewise, the left axillary lymph nodes drain into the left thoracic duct and then into the left subclavian vein via left *angulus venosus* [4]. However, anatomical studies have shown some major differences between the lymphatic drainages of the right and left sides. While the right lymphatic duct takes the lymphatic drainage of organs above the level of umbilicus and right hemithorax, right side of the head and neck and the right arm, the left lymphatic duct takes the lymphatic drainage of both lower extremities, left abdomen, left hemithorax, left side of the head and neck, and the left arm, thus covering approximately 3-fold greater area compared to the right side (Figure 1). The left lymphatic duct is 40 cm in length and 10 mm in diameter, while the right lymphatic duct is only 1-2 cm in length and 2-4 mm in diameter [4]. On the basis of these differences, theoretically, lymphatic flow in the left lymphatic duct should be higher in volume and faster compared to the right lymphatic duct, in order to maintain and compensate the drainage of about 3-fold larger area [5]. Whether such differences lead the right side to have more axillary lymph nodes compared with the left side is not yet fully investigated [6].

BC is the second most common cause of cancer-related deaths among women worldwide. About 231,840 new cases of BC in U.S. were expected to be diagnosed and an estimated number of 40,290 women and 440 men were expected to die of BC in 2015 [7]. During the last few years, a reduced mortality in BC survivors has been achieved by early disease detection methods [8]. Excluding treatment complications and adverse events, almost all of the deaths associated with BC are due to metastases. Therefore, understanding the metastatic pathways of BC is important in order to make a

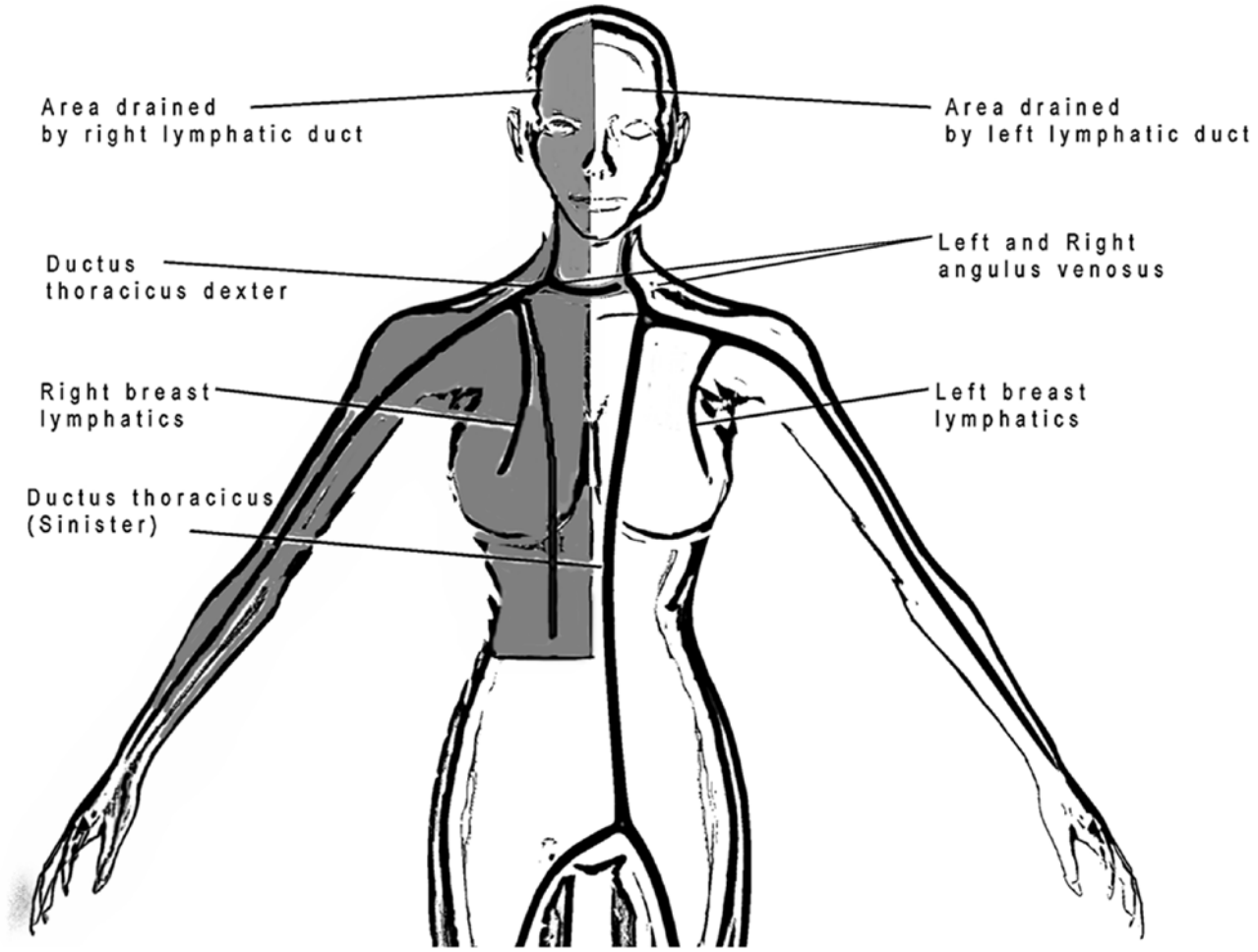

Figure 1. Differences of lymphatic drainage in right and left breast. The right lymphatic duct drains lymph from the right upper limb, right side of thorax, right arm and right halves of head & neck. The left lymphatic duct drains all body areas except those that drain the right lymphatic duct.

prediction regarding which patients will likely develop more frequent or earlier metastasis.

It has been shown that lymph node status is one of the most accurate prognostic factors in non-metastatic BC patients [9-11]. Indeed, irrespective of the histopathological features and T stage of the breast tumor, patients presenting with N3 stage have the highest risk for developing metastases. Because the systemic spread in BC generally occurs through lymphatic drainage, nodal involvement plays a central role for the development of metastases, hence it has an important impact on prognosis [9,10].

Approximately 29% of BC patients have nodal involvement or advanced disease at presentation [12]. According to the 7th edition of American Joint Committee on Cancer (AJCC), the pathological N3 (pN3) stage is divided into three subgroups: pN3a is defined as metastases in ≥10 ipsilateral axillary lymph nodes or metastases to the subclavicular nodes; pN3b is defined as metastases in ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive axillary lymph nodes or metastasis in clinically undetected internal mammary lymph nodes with micrometastases or macrometastases in the presence of metastases in >3 axillary lymph nodes; and pN3c represents metastases in ipsilateral supraclavicular lymph nodes [13].

As there is no significant variation between the right and left breast lymphatic drainage, the contribution of lymphatic flow to the development of metastases in left versus right BC hypothetically seems equal for N1 and N2 stages.

Anatomical difference between lymphatic flow of right and left breast begins beyond the N3 status.

The purpose of this study was to investigate if the difference of lymphatic flow between right and left breast has an effect on the pattern of metastatic disease and on survival of BC patients with pN3 nodal disease at presentation.

Methods

From a total of 4215 BC patients diagnosed between 1994 and 2015 in Hacettepe University Institute of Oncology, 305 operated patients with pN3 disease at presentation were identified and included in this study. All patients had level 3 axillary lymph node dissection along with their breast surgery and had postoperative pathological diagnosis of T1-4N3M0 (stage 3C). Estrogen receptor (ER) and progesterone receptor (PgR) nuclear staining with ≥1% was accepted as ER and/or PgR-positive by immunohistochemistry (IHC) evaluation. The evaluation of HER2 status was performed by using the standard scoring system of 0 to 3+, according to the membrane staining. Tumors scoring 2+ in IHC were analyzed by fluorescence *in situ* hybridization (FISH) test. Tumors were considered as HER2-positive in cases of either IHC 3+ score or FISH-amplified, and were considered as negative in case of either IHC 0 and 1+ score or non-FISH-amplified. Patients with bilateral BC, metastases or patients who received neoadjuvant therapy were excluded from the study. The patient demographic characteristics, localization and histopathological features of the tumor, T stage, number of involved lymph nodes, distant metastases, response to adjuvant treatment, and impact of tumor localization on TTM and OS were evaluated. The American Joint Committee on Cancer (AJCC) - 2010 staging system was used to determine the stage. Patient recent status was determined by the hospital records reporting system.

Statistics

All statistical analyses were performed using the Statistical Package for Social Sciences, version 18.0, for Windows (SPSS, Inc, Chicago, IL, USA). P values less than 0.05 were considered as statistically significant. The variables were examined according to the visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to identify if they were distributed normally or not. Descriptive statistics were specified as percentages and medians. Categorical variables were analyzed using the Chi-square or Fisher exact test. Kaplan-Meier method was used for survival analysis and log-rank test was used to compare the subgroups. OS was defined as the time from diagnosis to death or to the date of last visit. TTM was defined as the time from the date of primary surgery to first diagnosis of metastasis. The factors identified by univariate analyses as significant were subsequently entered into the Cox regression analysis with a backward selection to determine the independent predictors of survival.

Results

All patients included in the study were female. The mean age of 305 patients enrolled in this study was 48 years (range 20-92). Patient and tumor demographics are summarized in Table 1. Most of the patients (91%) had invasive ductal carcinoma. Of the 305 patients, 144 (47%) were premenopausal, 24 (8%) perimenopausal and 137 (45%) postmenopausal. Right-sided BC was diagnosed in 148 patients (48.5%) and the remaining 157 (51.5%) had left breast involvement. About 90% of the patients were administered chemotherapy with adriamycin + cyclophosphamide followed by paclitaxel and 73% of the patients were treated with hormone therapy. Adjuvant radio-

Table 1. Basic patient and tumor characteristics

Characteristics	*Right N=148 N (%)*	*Left N=157 N (%)*	*p value*
BMI (mean± SD)	28.2±5.15	27.6±5.13	0.33
Menopausal status			
Premenopausal	78 (52.7)	90 (57.3)	0.41
Postmenopausal	70 (47.3)	67 (42.7)	
Medication history			
Oral contraceptive	37 (25.0)	40 (25.5)	0.92
Hormone replacement treatment	25 (16.9)	13 (8.3)	0.02
Chronic diseases			
DM	19 (12.8)	18 (11.5)	0.71
HT	36 (24.3)	37 (23.6)	0.87
CAD	4 (2.7)	1 (0.6)	0.15
Thyroid	19 (12.8)	22 (14)	0.76
Age at first menstruation, median (range)	13 (10-17)	13 (9-17)	0.80
Age at first birth, median (range)	22.5 (15-39)	22 (14-39)	0.60
Age at diagnosis, median (range)	49 (25-78)	47 (20-92)	0.18
Breast-feeding	127 (85.8)	131 (83.4)	0.60
Site of tumor			
Outer half	104 (72.2)	109 (71.7)	
Inner half	23 (16.0)	29 (19.1)	
Central area	5 (3.5)	5 (3.3)	0.79
Multifocal	12 (8.3)	9 (5.9)	
Histology			
IDC	140 (94.6)	137 (87.3)	0.02
ILC	8 (5.4)	20 (12.7)	
Grade			
1	8 (5.7)	7 (4.9)	0.85
2	60 (42.6)	57 (40.1)	
3	73 (51.8)	78 (54.9)	
Tumor subgroup			0.66
Luminal A	74 (50.0)	86 (54.8)	
Luminal B	34 (23.0)	31 (19.7)	
HER2 type*	15 (10.1)	19 (12.1)	
Triple negative	25 (16.9)	21 (13.4)	
Pathologic features			
ECE	86 (58.1)	84 (53.5)	0.45
PNI	14 (9.5)	15 (9.6)	0.96
LVI	83 (56.1)	80 (50.9)	0.40
T stage			0.04
T1	18 (12.2)	37 (23.6)	
T2	78 (53.1)	74 (47.1)	
T3	49 (33.3)	46 (29.3)	
T4	2 (1.4)	0	
Lymph node involvement, median (range)	14 (9-64)	14 (9-40)	0.74
Lymph node ratio, median (range)	0.66 (0.19-1)	0.66 (0.25-1)	0,37
Chemotherapy			
AC+T	136 (91.9)	137 (87.3)	0.16
Other	12 (8.1)	17 (10.8)	
None	0	3 (1.9)	
Hormonotherapy			0.05
Tmx	48 (44.4)	55 (47.0)	
AI	50 (46.3)	39 (33.3)	
Switch (Tmx - AI)	10 (9.3)	20 (17.1)	

BMI: body mass index, SD: standard deviation, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, IDC: invasive ductal cancer, ILC: invasive lobular cancer, ECE: extra capsular extension, PNI: perineural invasion, LVI: lymphovascular invasion, AC+T: adriamycin + cyclophosphamide with / followed by paclitaxel or docetaxel, Tmx: Tamoxifen, AI: aromatase inhibitors
*ER negative, PR negative, HER2 positive

Table 2. The differences in metastasis between right and left breast

Metastatic patients	*Right N=53 N (%)*	*Left N=70 N (%)*	*p value*
Site of metastasis			
Skin	5 (9.4)	7 (10)	0.85
Cervical lymph node	9 (17)	5 (7.1)	0.08
Axial bones	19 (35.8)	39 (55.7)	0.02
Liver	12 (22.6)	18 (25.7)	0.69
Lung	14 (26.4)	16 (22.9)	0.64
Brain	5 (9.4)	6 (8.6)	0.83
Ovary	2 (3.7)	2(2.8)	0.31

therapy was delivered to 298 (97.7%) patients.

The pattern of metastatic disease in patients who had distant recurrences (N=123;40%) after a median follow-up time of 43.7 months (interquartile ratio/IQR 18.6-68.4) were as follows: skin N=12 (9.7%); cervical lymphadenopathy N=14 (11%); axial skeleton (vertebrae, sacrum, pelvis) N=58 (47%); liver N=30 (24%); lung N=30 (24%); brain N=11 (9%); and ovary N=4 (3.2%). Comparative results of the patients are shown in Table 2. The number of local recurrences on both sides (right N=12 vs left N=15, p=0.67) showed no significant difference and were not included in metastatic TTM calculations. There was no statistically significant difference between the groups in terms of menopausal status, age at diagnosis, tumor grade, hormone receptor status, number of metastatic lymph node and the median lymph node ratio (number of metastatic lymph node / total number of excised lymph node) (p=0.63, p=0.18, p=0.85, p=0.57, p=0.74, p=0.37, respectively).

Patients with left BC had significantly more invasive lobular malignancy and smaller T stage compared with the right BC group (12.7 vs 5.4%, p=0.02; T1 stage 23.6 vs 12.2%, p=0.04, respectively). Approximately 35% of patients with right BC and 45% of patients with left BC developed metastases during follow-up. While axial bone metastases were significantly more common in patients with left BC (55.7 vs 35.8%; p=0.02), visceral metastases were similar in both groups (Table 2). During the follow-up period, 31 deaths among the right-sided BC patients and 27 deaths in left-sided group occurred. Median TTM was 59.5 months (95% CI: 45-74) and the median OS was 135 months in all patients (95% CI: 103-168). Median TTM was significantly greater in the right group [103.6 (95% CI 47.0-160.2) vs 49.1 months (95%CI 36.5-61.8), p=0.03] and no distinctive difference in OS was found between the groups [151.9 (95% CI 55.3-248.5) vs 129.1 months (95% CI 113.3-145.0), p=0.68] (Table 3, Figure 2a and Figure 2b).

Premenopause (p=0.04), age <35 years (p<0.01), PR negativity (p=0.03), ER negativity (p=0.04), tamoxifen only group (p<0.01), cancer in the left breast (p=0.03) were adversely associated with inferior TTM in univariate analysis. No correlation was found between body mass index (BMI), tumor subgroup, histology, grade, HER-2 status, lymphovascular invasion, perineural invasion, extracapsular extension in lymph nodes, T stage,

Table 3. Univariate and multivariate analysis of factors associated with TTM

Variables	*Median TTM, months*	*Univariate P*	*Multivariate P*	*HR (95% CI)*
Menopause				
Premenopausal Postmenopausal	49.1 71.9	0.04	0.66	
Age (years)				
≤35	33.0	<0.01	0.88	
>35	68.2			
ER status				
Negative	39.4	0.04	0.63	
Positive	62.9			
PR status				
Negative	37.0	0.03	0.52	
Positive	67.3			
Laterality				
Right	103.6	0.03	0.03	1.6 (1.04-2.54)
Left	49.1			
Hormonotherapy				
Switch (Indicator)	140.5			
AI	68.2		0.08	
Tmx	41.0	<0.01	<0.01	4.4 (2.18-8.98)

TTM: time to first metastasis, ER: estrogen receptor, PR: progesterone receptor, Tmx: tamoxifen, AI: aromatase inhibitors, HR: hazard ratio, CI: confidence interval. HR: hazard ratio provides a 95% confidence interval

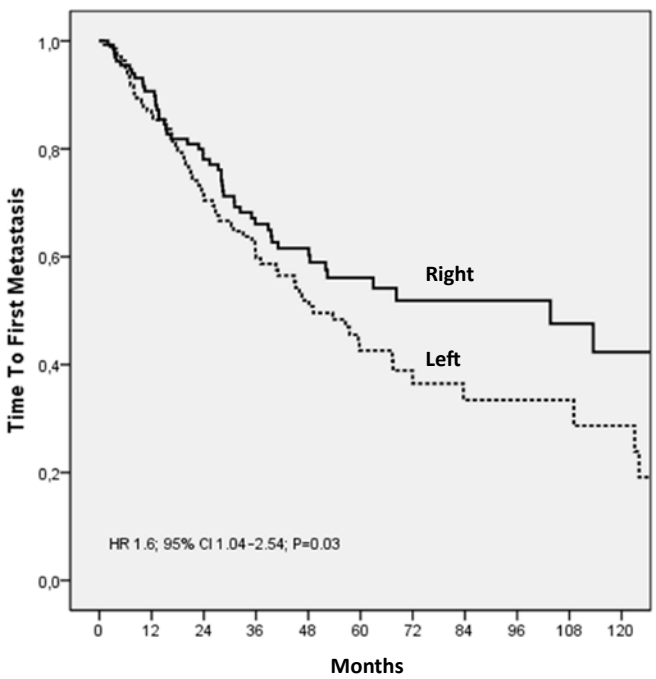

Figure 2a. Time to first metastasis in both right and left groups.

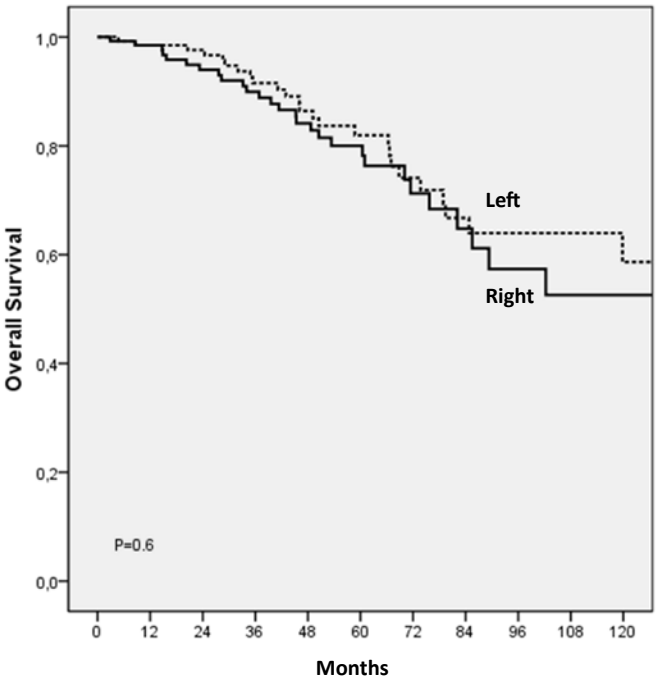

Figure 2b. Overall survival in both right and left groups.

lymph node ratio, chemotherapy and TTM in univariate analysis. Patients with right BC switching to hormone therapy showed a low recurrence risk in multivariate analysis (Table 3).

Grade 3 differentiation (p=0.01), ER negativity (p=0.03), tamoxifen only group (p<0.01) and BMI ≥25 (p=0.01) were associated with significantly lower OS in univariate analysis. BMI was found to be independent prognostic factor significantly associated with OS (BMI ≥ 25 vs BMI < 25; HR 4.9; 95% CI 1.41–17.23; p=0.01).

Discussion

Malignancies arising from paired organs on the right or left half of the body may have different clinical outcomes and different mechanisms have been suggested to explain this issue. One hypothesis investigated was that the difference in size and anatomical organ asymmetry might affect the development of cancer and its prognosis. Roychoudhuri et al. investigated the effect of cancer laterality on the incidence, stage at diagnosis and survival in 5 major paired organs including the breast, lung, kidney, testis and ovary. In that study, patients with left testicular cancer, right lung cancer and left ovarian cancer were found to have significantly better survival than the contralateral disease (p<0.05). However, the authors reported no significant difference in BC [3]. In contrast to our study design, the above mentioned study evaluated all stages of BC patients.

Another point of view for laterality is that cancer may have different clinical characteristics and behavioral patterns, depending on the dominant side of the brain hemisphere [14,15].

In a retrospective study analyzing the BC laterality in 234,657 patients, the overall rates of left to right-sided invasive tumors in women were 1.05 and this increase was statistically significant (p<0.001); however, there was no conspicuous variation in the laterality of invasive disease over time, the left-sided increase was prominently higher during the time interval of 1978-82, compared with other time periods [16].

In the present study tumor grade, molecular subtypes, presence of lymphovascular invasion, presence of extranodal involvement, the number of involved lymph nodes and type of treatment were similar in both groups. The only significant difference was that there were more invasive lobular cancers in the left breast group (p=0.02) and that the T stage was higher in the right breast cancer group (p=0.04). It is well known that T stage is an important prognostic factor in BC [10]. An interesting finding was that despite the higher T stage in the right BC group, patients with left BC developed a significantly higher rate of overall distant metastases and had shorter TTM, supporting our hypothesis of the negative effect of laterality.

On the other hand, the most crucial step for

the development of systemic metastasis in BC is the presence of nodal involvement, regardless of tumor size [17,18]. We hypothesized that clinical variations related to laterality may be partly due to the following factors: different number of involved lymph nodes in each half of the body and/or different lymphatic flow between the right and left side. As previously stated, the left lymphatic duct, which takes the lymphatic flow of the left breast, takes also the lymphatic drainage of lower extremities, left abdomen, left hemithorax, left side of the head and neck and the left arm, amounting to drainage of 3-fold greater area compared to that of the right lymphatic duct, whereas the right lymphatic duct, which drains the right breast, only receives the lymphatics of the organs above the level of umbilicus and right hemithorax, right side of the head and neck and the right arm. In addition, the right lymphatic duct is much shorter and has a simpler structure compared to thes left lymphatic duct [19].

In a retrospective study based on Surveillance, Epidemiology and End Results (SEER) database, evaluating the importance of BC laterality in 305,443 patients, laterality was found to have no significant effect on OS [20]. However, in that study patients with central portion breast cancer had significantly shorter survival in left-sided tumors in sub-group analysis and it was also stated that this difference may be due to the possible effects of lymphatic asymmetry (95% CI, HR, 1.100; p=0.013, using the right side as reference). The authors reported that rather than laterality, the tumor location had a stronger effect on OS. The upper-outer quadrant tumors on both sides, and the right central tumors had the best prognosis, while tumors in the inner region on both sides showed poorer prognosis. In our study, however, we focused only on patients with high nodal disease burden (pN3, M0), suggesting that the lymphatic drainage differences between the right and left breast begin beyond the axillary level, therefore we included only patients with N3 disease but without distant metastasis, with the goal of detecting the effect of laterality on TTM or OS – if any – in those patients who had the highest risk of developing metastasis. Although SEER analysis included a large number of samples, the patient selection in our study was more optimal in order to investigate the importance of laterality in terms of the lymphatic asymmetry. Because SEER analysis also included N0, N1 and N2 patients, this effect might have been lowered.

It is documented that the lymphatic flow in the right lymphatic duct is reduced compared to the left side [5]. Therefore, it may be hypothesized that a neoplastic cell which goes through the left lymphatic flow has a higher likelihood of passing into the systemic circulation due to rapid flow, thus may be associated with an increased risk of earlier metastases compared to right BC. In the present study, we included patients with high nodal disease burden (pN3) with the assumption that lymphatic drainage is equal for both right and left breasts and both axillae, which is also the final step for a malignant cell to leave the lymphatics and enter the blood circulation. Anatomical differences of right and left breast become significant above the level of the axilla, hence only patients with N3 disease were included in this study. In our series, there was an equal pN3 ratio noted for both right and left BC groups. However, the TTM in the left-sided group was associated with a trend towards decreased survival, but there was no significant difference in OS between the two groups despite the fact that the number of patients with higher T stages was less in this group compared to that of right-sided group.

It may also be hypothesized that, lymphatic obstruction due to internal mammary lymph node involvement or severe axillary nodal involvement may partly lead to different pathways in metastatic spread by backflow in lymphatic drainage. On this subject, Haagensen had suggested in 1972 that lymphatic metastasis could be possible by a retrograde flow [21]. Likewise, Vermeeren et al. confirmed the theory of retrograde lymphatic flow with a lympho-scintigraphic study [22]. Sood et al. also confirmed the backflow in internal mammary lymph nodes by a lympho-scintigraphic method in BC patients who developed recurrences and distant metastases following axillary lymph node dissection [23]. Herein, on the basis of the results in this study, a significant association of left laterality in axial bone metastasis may support this theory.

Today, scintigraphic studies conducted for showing the lymphatic drainage pathway of the SLN are terminated as soon as the blue dye or radioactive material reaches the axilla. The speed of lymphatic flow of each breast to subclavian vein or to systemic circulation is still not known.

Herein we found that left BC patients with pN3 disease at presentation had significantly reduced TTM. While the difference in OS of both groups was not statistically significant, this can be attributed to smaller T stages on the left side or to relatively short follow-up time (median follow up

time was 43.7 months). We acknowledge, as a limitation, that the effects of laterality need to be explored in a much larger population. While we have selected our study group among 4215 BC patients, we had the advantage that our oncology hospital serves as a tertiary unit to central Turkey and advanced cases (pN3) were relatively more common compared to many district hospitals or screening units. Also, by limiting the selection to pN3, M0 patients from our database we aimed to enhance the possible effects of laterality to maximum level as the anatomical differences start beyond the axillae. To the best of our knowledge there are no studies in the literature investigating the significance of laterality in this selected group of patients with histopathologic features and T stage data.

Conflict of interests

The authors declare no confict of interests.

References

1. Akbay E, Cayan S, Doruk E, Duce M, Bozlu M. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. BJU Int 2000;86:490-493.
2. Mine S, Yamada K, Grabsch H et al. The prognostic significance of tumor laterality in patients with esophageal squamous cell carcinoma. J Surg Oncol 2012;105:66-70.
3. Roychoudhuri R, Putcha V, Møller H. Cancer and laterality: a study of the five major paired organs. Cancer Causes Control 2006;17:655-662.
4. Tanis PJ, Nieweg OE (Eds): The Anatomy and Physiology of Lymphatic Circulation. Atlas of Lymphoscintigraphy and Sentinel Node Mapping. Springer, 2013, pp 1-5.
5. Földi M, Strössenreuther RH (Eds): Foundations of manual lymph drainage (3rd Edn). 2004, Elsevier, New York.
6. Cappello F, Bellafiore M, Palma A et al. Study of axillary lymph node asymmetry in a female population. J Anatomy 2001;199:617-620.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: Cancer J Clin 2015;65:5-29.
8. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380:1778-1786.
9. Comen EA, Norton L, Massagué J. Breast cancer tumor size, nodal status, and prognosis: biology trumps anatomy. J Clin Oncol 2011;29:2610-2612.
10. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63:181-187.
11. Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. Breast Cancer Res Treat 1999;56:67-78.
12. Amonkar S, Oates E, McLean L, Nicholson S. Pre-operative staging of the axilla in primary breast cancer. By redefining the abnormal appearing node can we reduce investigations without affecting overall treatment? The Breast 2013;22:1114-1118.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual: Springer New York; 2010.
14. Sandson T, Wen P, LeMay M. Reversed cerebral asymmetry in women with breast cancer. Lancet 1992;339:523-524.
15. Titus-Ernstoff L, Newcomb PA, Egan KM et al. Left-handedness in relation to breast cancer risk in postmenopausal women. Epidemiology 2000;11:181-184.
16. Weiss HA, Devesa SS, Brinton LA. Laterality of breast cancer in the United States. Cancer Causes Control 1996;7:539-543.
17. Hernandez-Aya LF, Chavez-MacGregor M, Lei X et al. Nodal status and clinical outcomes in a large cohort of patients with triple-negative breast cancer. J Clin Oncol 2011;29:2628-2634.
18. Senkus E, Kyriakides S, Penault-Llorca F et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 (Suppl 6): 7-23.
19. Skandalakis JE, Skandalakis LJ, Skandalakis PN. Anatomy of the lymphatics. Surg Oncol Clin North Am 2007;16:1-16.
20. Bao J, Yu K-D, Jiang Y-Z, Shao Z-M, Di G-H. The Effect of Laterality and Primary Tumor Site on Cancer-Specific Mortality in Breast Cancer: A SEER Population-Based Study. PloS One 2014;9(4):e94815.
21. Haagensen CD. Lymphatics of the breast. In: Haagensen CD, Freind KR, Herter FP, Slanetz CA, Weinberg JA: The lymphatics in cancer. Philadelphia, WB Saunders Co, 1972, pp 300-387.
22. Vermeeren L, Tanis P, Nieweg O, Olmos RV. Lymphoscintigraphy of a breast tumor showing focal tracer accumulation along the falciform ligament of the liver. Clin Nucl Med 2010;35:168-169.
23. Sood A, Youssef IM, Heiba SI et al. Alternative lymphatic pathway after previous axillary node dissection in recurrent/primary breast cancer. Clin Nucl Med 2004;29:698-702.