RESEARCH ARTICLE

Lymph Node Ratio Assessment of Brain Metastasis in Early Breast Cancer Cases

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Abstract

Background: Ten to 30% of early breast cancer (EBC) patients develop brain metastasis (BM) during their follow-up. In this study, we aimed to evaluate importance of the lymph node ratio (LNR) in development of BM in EBC cases. Materials and Methods: Ninety patients whom had axillary metastases in lymph nodes at their initial diagnosis and developed BM during 5-year follow-up were detected in 950 EBC patients. LNR values were calculated for all patients and after categorization into 4 molecular sub-types as luminal A, luminal B HER-2 (+), HER-2 overexpressing and basal- like. Comparison was with control group patients who had similar characteristics. Results: In the comparison of all molecular sub-types of LNR, 54.9% and 28.4% values were found in patients with and without BM respectively (p<0.001). In the comparison of the LNR with control groups, a statistically significant differences were found with luminal A with BM (p=0.001), luminal B HER-2 (p=0.001), HER-2 overexpressing (p=0.027) and basal-like groups (p<0.001). In the evaluation of patients with BM, the highest ratio was found in the basal-like group (67.9%) and there was a statistically significant difference between this group and the others (p=0.048). Conclusions: EBC patients developing BM within 5 years follow-up had significantly higher LNRs for all molecular sub-types, especially in the basal-like group. Larger scale studies are now needed for evaluating LNR prognostic importance for EBC regarding BM development.

Keywords: Early breast cancer - brain metastasis - lymph node ratio - prognosis

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Introduction

Ten to 30% of early breast cancer patients (EBC) develop central nervous system metastasis during their follow-up (Barnholtz-Sloan et al., 2004; Lin et al., 2004). Brain metastasis (BM) is one of the most important factor for survival of the patients with breast cancer. Despite local and systemic treatments, median overall survival (OS) of patients is 5 months and 1 year OS ratio is 20% for all breast cancer types (Engel et al., 2003; Lin et al., 2004). In addition tumour size, nodal expansion, estrogen receptor (ER) status, progesterone receptor (PR) status and human epidermal growth factor receptor 2 (HER-2) expression are the most important risk factors for development of metastasis (Alanko et al., 1985; Chia et al., 2008).

There have been significant studies related with the axillary lymphatic evaluation of EBC in recent years (Woodward et al., 2006; Hatoum et al., 2009; Vinh-Hung et al., 2009; Goldhirsch et al., 2011). Besides the heterogeneity of the disease, the American Joint Committee on Cancer (AJCC) grading system classify lymph nodes over merely the number of involved lymph node and in large groups (Greene et al., 2002). Therefore the lymph node ratio (LNR) that is determined as the ratio of metastatic lymph nodes to the total removed lymph nodes coming up. In many studies, it was indicated that LNR is able to evaluate lymphatic metastases in a very delicate and superior way (Woodward et al., 2006; Hatoum et al., 2009; Vinh-Hung et al., 2009; Li et al., 2012). However there is no research study into the relation between BM and LNR. Molecular classification of breast cancer is widely used in the clinic (Goldhirsch et al., 2011). In this purpose, the LNR differences based on molecular subtype of the EBC patients who had developed BM in 5 years during their follow-up compared to control group in the current study.

Materials and Methods

In this study, the data of the breast cancer patients who were treated with adjuvant intent between 2001 and 2010 at Gazi University, Faculty of Medicine, were retrospectively analyzed. Out of 950 patients with EBC, 105 patients who were detected BM within 5 years from

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their diagnosis were chosen. In order to detect LNR in this patient group, 90 patients with metastatic axillary lymph node were included in the study. LNRs were calculated using the formula of [(metastatic lymph node number/ total dissected lymph node number) x 100] and given as percentages. Following that, the patients were divided into four molecular sub-types depending on ER, PR and HER-2 status.

In order to make a comparison of LNR, control groups were choosen from patients with similar average tumour sizes and ages and same molecular sub-types besides whom did not have any relapse or distant metastasis in their follow-ups. For each molecular sub-type, mean LNRs in the group with and without BM were compared with each other using an "Independent samples t test". Afterwards the difference between sub-types of metastatic group was examined through variance analysis (one-way anova). In the analysis of the statistics, the package program of SPSS 16.0 version was used and $p<0.05$ value was regarded as statistically significant.

Results

The patients diagnosed as EBC and treated with adjuvant therapy in addition developed BM within 5-years during their follow-up were grouped as ER (+) and/or PR (+), HER-2 (-) and grade 1 were included in Luminal A group (n=14), ER (+) and/or PR (+), HER-2 (+) were included in Luminal B HER-2 (+) group (n=24), ER (-), PR (-), HER-2 (+) were included in HER-2 over expression type group (n=28) and finally patients with triple negative molecular indicators were included in basal like type group (n=24). The patients with similar features (molecular sub-type, tumour size and age) who had treated with EBC but not detected relapse or metastasis were chosen as the control group. The data of the control group and the metastatic group are shown in Table 1. The mean age was 58.5 (35-94) and the mean tumour size was 4 cm in the patients with BM in all molecular sub-types; the mean age was 58.3 (31-82) and mean tumour size was 3.99 in the control group. In the LNR comparison of the two groups, 55% and 28.5% rates were obtained respectively ($p<0.001$).

With the comparison of LNRs, statistically significant value was obtained as 51.7% in the Luminal A with BM patients and 16.2% in the control group ($p=0.001$). Similarly statistically significant values for Luminal B HER-2 (+) group with BM and the control group upon 50% and 26.3% were detected respectively ($p=0.001$).

Table 1. Patient Characteristics

	n	Age	Tumor Size	Total LN	Metastatic LN	LNR (%)
BM- Luminal A	14	59.0	5.49	19.7	9.43	51.7
BM- Luminal B HER-2	24	58.3	4.99	20.9	10.50	50.0
BM-HER2	28	61.2	3.20	20.2	9.86	49.8
BM- Bazal like	24	55.2	3.09	18.7	12.80	67.9
Control Luminal A	14	59.1	5.50	18.7	2.93	16.2
Control Luminal B HER-2	24	57.7	4.98	18.2	4.50	26.3
Control HER2	28	60.7	3.19	22.6	7.96	34.4
Control Bazal like	24	55.3	3.07	17.5	4.29	30.9

*BM, Brain metastasis; LN, Lymph node; LNR, Lymph node ratio

Table 2. Lymph Node Ratio According to Groups

	n	Mean LNR (%)	Std. Deviation (Min-Max)	p
BM- Luminal A	14	51.7	28.6 (2.2-89.5)	0.001.
Control- Luminal A	14	16.2	15.1 (3.4-52.9)	
BM- Luminal B HER-2	24	50	24.0 (4.8-100)	0.001.
Control- Luminal B HER-2	24	26.3	24.0 (4-100)	
BM- HER2	28	49.8	26.2 (8-100)	0.027.
Control- HER-2	28	34.4	24.4 (2.1-100)	
BM- Basal like	24	67.9	25.5 (5.9-100)	<0.001
Control- Basal like	24	30.9	29.5 (2.8-100)	

*BM, Brain metastasis; LN, Lymph node; LNR, Lymph node ratio

With the comparison of LNRs in the HER-2 over expression group with BM and the control group, a statistically significant difference was obtained with the values of 49.8% and 34.4% respectively ($p=0.027$). In the basal like group, the LNRs of the patients with BM and the control group were 67.9% and 30.9% respectively ($p<0.001$). In the evaluation of the LNRs of the patients with BM depending on their molecular sub-types, the highest ratio was found in the basal like group (67.9%) and a statistically significant difference obtained between the other groups ($p=0.048$). Then, LNRs were 51.7% in Luminal A group, 50% in Luminal B HER-2 (+) group and 49.8% in HER-2 over expression group. The LNRs of the patients with BM and the control group according to molecular sub-types are given in Table 2.

Discussion

Axilliary lymph node involvement is one of the most important factor that affects the breast cancer staging, treatment and outcome. The BM risk is increased dramatically in the case of involved lymph node detection during diagnosis (Alanko et al., 1985; Chia et al., 2008). In recent studies, LNR has been revealed as exhibiting more delicate information in the lymphatic evaluation (Woodward et al., 2006; Hatoum et al., 2009; Vinh-Hung et al., 2009; Goldhirsch et al., 2011, Li et al., 2012). In our study, the effect of LNR on developing BM in EBC patients was examined in order to add a different dimension to this relation.

In this study, a significant increase was shown on LNR in the breast cancer patients whom were developed BM within 5 years follow-up whom compared with non-metastatic patients having same characteristics. This finding contributes to the literature for the prognostic value of LNR. Vinh-Hung et al., defined two cut-off values for LNR as 20% and 65% (Vinh-Hung et al., 2009). In our study LNR was found 55% in patients with BM and 28.5% in the control group so both values were regarded as the medium risk according to Vinh-Hung et al. (2009). There is no consensus over determining LNR cut-off values yet. In order to increase the sensitivity of the LNR that is thought to be an alternative grading system and could give more correct data compared to AJCC grading system, randomized studies to detect new cut-off value definitions would be beneficial for clear definitions.

In present study, the highest rate at the evaluation of LNR according to the molecular sub-types was in the basal like type with 67.9%. Kennecke et al. carried out a study

to determine the metastatic behaviours of the sub-types at breast cancer and found that basal like tumours caused more brain, lung and distant lymphatic metastasis, while liver and bone metastasis were observed less frequently (Kennecke et al., 2010). In addition, it was pointed out that HER-2 positivity was related with increased brain, liver and lung metastasis (Kennecke et al., 2010; Dayan et al., 2012). In our study, LNR difference in basal like type is statistically significant and this finding is consistent with the literature. However, out of the groups exhibiting HER-2 positivity, LNR was found 50%in the Luminal B HER-2 (+) group, 49.8% in the HER-2 over expression group and no significant difference was found when compared to Luminal A group with a LNR of 51.7%. It was striking that the number of patients in Luminal A group (n=14) were less than other groups and this finding was consistent with the literature. In addition, there have been many studies showing that ER and/or PR secretion reduces the risk of metastatic disease (Hoefnagel et al., 2010; Karlsson et al., 2010; Gong et al., 2011; Ziaei et al., 2012). Another important factor in the current study was the difference between the molecular sub-types and mean tumour sizes at the patients with BM. In the groups Luminal A and Luminal B that determined ER and/or PR expression, 5.49 and 4.99 cm mean tumour sizes were observed respectively; while they were 3.2 and 3.09 cm in the HER-2 over expression and basal like groups where the hormone receptors (HR) were negative respectively. Development of BM in the Luminal A and B groups, with longer size of tumor is thought to be related with the protective effect of HR. The limitations of the study were its retrospective nature, relatively fewer number of patients and not including treatment and survival data were not able to be included in the study.

The patients developing BM in 5 years during their follow-up had significantly higher LNRs for all molecular sub-types compared to control patients. This finding is important for contribution to staging however, due to the fact that definitions were made in a large interval for the mid-risk group in the earlier studies, it is necessary that a LNR cut-off values should be determined in smaller intervals in detail for a delicate grading. In addition the highest LNR is seen in basal like group. This group should be followed more carefully because of more aggressive course compared to other molecular sub-types. In addition, it should be considered that smaller sized tumours could exhibit metastatic behaviours in the hormone receptor negative tumours. Larger scale studies are needed for evaluating LNR consequence at prognostic importance in BM development of EBC.

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