Int J Clin Exp Med 2015;8(10):17789-17795
www.ijcem.com /ISSN:1940-5901/IJCEM0012313

Original Article

Correlation of lymphovascular invasion with clinicopathological factors in invasive breast cancer: a meta-analysis

San-Di Shen[1,2], Shi-Zhen Zhong[1], Chun-Zhong Wang[3], Wen-Hua Huang[1]

[1]Department of Human Anatomy, School of Basic Medicine Science, Southern Medical University, Guangzhou, P. R. China; [2]Headneck & Breast Surgery, Yuebei People 's Hospital, Shaoguan, P. R. China; [3]Department of General Surgery, The First Municipal Hospital of Guangzhou, Guangzhou, P. R. China

Received July 2, 2015; Accepted October 9, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Objectives: Lymphovascular invasion (LVI) has been associated with a poor outcome in patients with breast cancer, but it is not included in international TNM staging system and molecular subtype criterion. The current studies have reported the relation between LVI and the tumor size (T), the status of axillary lymph node (ALN), age, histological grade in invasive breast cancer, but the results were debatable. So the meta-analysis was conducted to confirm the relation between LVI and the four clinicopathological factors. Methods: Literature was searched by entering the terms: breast AND (neoplasm OR cancer OR carcinoma) AND (lymphovascular OR "lymphatic vessel" OR "vascular vessel" OR "blood vessel" OR "lymph vessel") AND (invasion OR "carcinoma embolus") AND (lymph node OR grade OR size OR clinicopathological) in PubMed, The merged odds ratio (OR) and 95% confidence interval (CI) were estimated using fixed-effect or random-effect model, RevMan 5.3 was used to analyze the relation between LVI and tumor size, status of ALN, age, histological grade in invasive breast cancer respectively. The fail-safe number was used to estimate publication bias. Results: The analysis included 6 studies, LVI positive rate was significant lower in T≤2 cm, ALN negative, age >50 y and histological grade 1 groups statistically. The OR and 95% CI were 0.53 [0.46, 0.61], 0.23 [0.15, 0.35], 1.62 [1.42, 1.85], 0.36 [0.17, 0.77] respectively. Conclusions: LVI was significantly correlated with the expression status of the tumor size, status of ALN, age, histological grade in invasive breast cancer, and was consistent with adverse features of the four factors.

Keywords: Lymphovascular invasion, histological grade, axillary lymph node, clinicopathological factors, breast cancer

Introduction

Breast cancer is a common cancer and one of the leading causes of cancer death in female. It accounts for 29% of all female new cancers and 15% of all female deaths due to cancers [1]. LVI is a key step of tumor cells reaching lymph node, therefore, LVI has been known as an independent predictor of lymph node metastases. Lymph node positive breast cancer has a poor prognosis. In breast cancer, LVI has been as an independent predictor of disease-free survival (DFS) as well as overall survival (OS) [2, 3]. The 2005 St. Gallen consensus guidelines suggested LVI was recognized as one of the factors upon which to base treatment plan decisions [4].

LVI is assessed in the carcinoma tissue on hematoxylin and eosin (H&E) stained sections, it is defined as carcinoma cells present within a definite endothelial-lined space (lymphatic or blood vessel). So LVI include lymphatic and blood vessel invasion. Routine assessment of LVI is now part of breast cancer pathology reporting.

The prognosis of breast cancer varies with different TNM stage, age, histological grade. The current studies have reported the relation between LVI and the four factors in invasive breast cancer, but the results were disputed [5-10]. So this meta-analysis was conducted to confirm the correlation between LVI and the tumor size, the status of ALN, age, and histological grade.

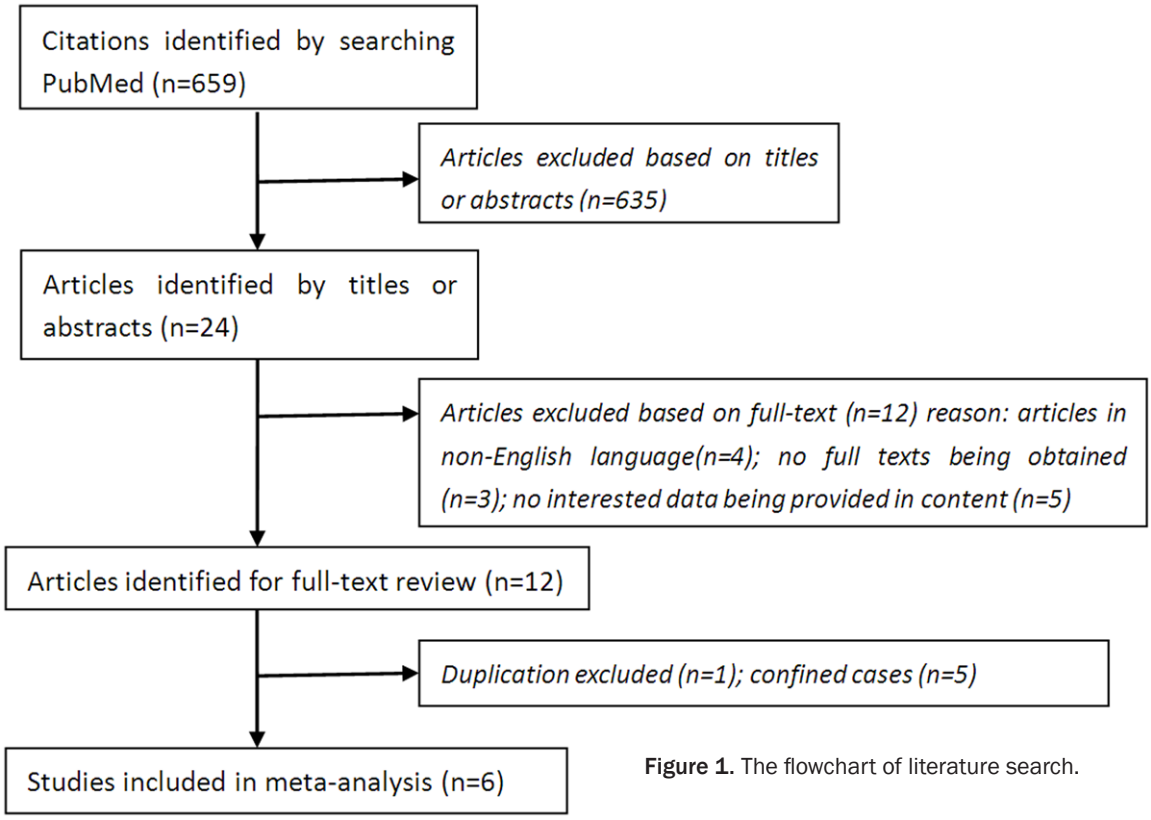

Figure 1. The flowchart of literature search.

Materials and methods

Literature search strategy

Literature was searched by entering the terms: breast AND (neoplasm OR cancer OR carcinoma) AND (lymphovascular OR "lymphatic vessel" OR "vascular vessel" OR "blood vessel" OR "lymph vessel") AND (invasion OR "carcinoma embolus") AND (lymph node OR grade OR size OR clinicopathological) in PubMed. The publish time of literature was unlimited. Only literature written in English language was included.

Inclusion criteria

All of the following criteria had to be included in literature for this analysis: (1) Patients with breast cancer were not subjected to radiotherapy, hormone therapy and chemotherapy before the pathological specimen were extracted. (2) The stages of the disease were $T_{1-4}N_{0-3}M_{0-1}$ or I-IV stages. (3) LVI was determined by H&E staining. (4) All literature was in English language.

Exclusion criteria

The literature in which the detection method of the LVI was not H&E, or from which the interested data could not be extracted was excluded.

Data extraction

The following information was extracted from each eligible literature: authors' names, year of publication, the tumor size, the status of ALN, age, histological grade, case date, study location and LVI positive rate in each group.

Statistical analysis

RevMan 5.3 software was used to perform the meta-analysis. The OR and 95% CI were used to estimate the correlation of LVI and clinicopathological factors in the invasive breast cancer. The Mantel-Haenszel method was used to combine the ORs for the outcomes. The fixed-effect or random-effect model was used to calculate the pooled outcome according to heterogeneity. Each study was weighted according to the sample size. The heterogeneity among studies was defined significant when $P<0.1$ for χ^2 test or $I^2>50\%$. Fail-safe number was used for detecting publication bias according to the formula $N_{fs0.05}=(\Sigma Z/1.64)^2-K$.

Table 1. The characteristic of cases in invasive breast cancer in included studies

Characteristic of cases	LVI positive rate (no./cases)					
	Gujam FJ 2014	Lee JA 2011	Rakha EA 2012	Tezuka K 2007	Aitken E 2010	Wu JL 2014
Tumor size (cm)						
≤2	38/185	1/41	559/1884	17/44		
>2	64/175	4/39	536/1232	50/88		
ALN status						
negative	41/206	0/41	443/2426	24/63	70/398	157/742
positive	61/154	5/39	683/1341	43/69	98/225	416/583
Age (years)						
≤50	39/125	1/38	565/1572	26/42		
>50	63/235	4/42	563/2236	41/90		
Histological grade						
1	10/48	0/15	72/622			
2/3	92/312	5/63	899/2633			
Date	1995 to 1998	2005 to 2007	1989 to 2004	1997 to 2000	2003 to 2005	2004 to 2010
Location	Royal Infirmary, Western Infirmary, Victoria or Stobhill Hospitals Glasgow	Korea University Anam Hospital Seoul	Nottingham City Hospital Nottingham	Osaka City University Hospital Osaka	Crosshouse Hospital, Kilmarnock Ayrshire & Arran	Changhua Christian Hospital Taiwan

ALN: axillary lymph node; LVI: lymphovascular invasion.

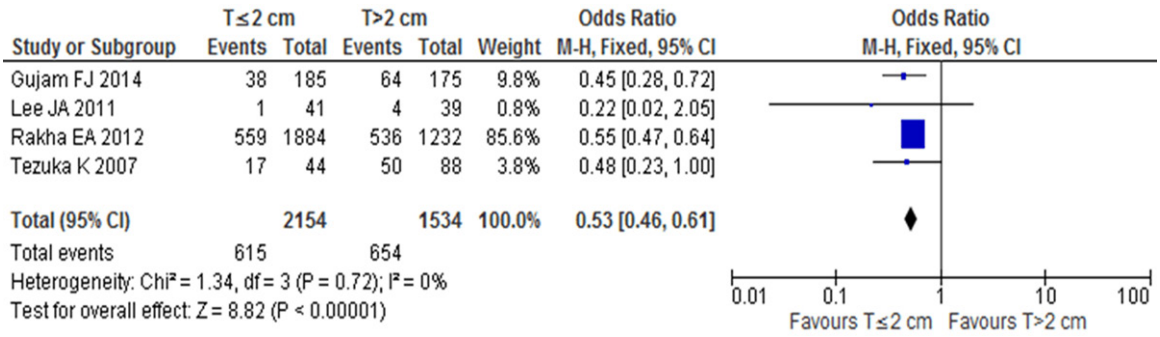

Figure 2. LVI positive rates between T≤2 cm and T>2 cm groups in invasive breast cancer.

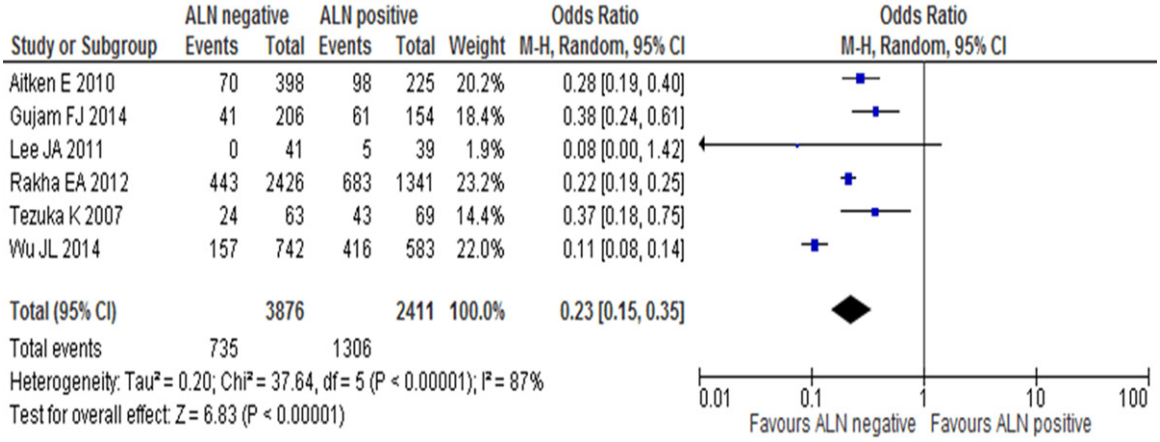

Figure 3. LVI positive rates between ALN negative and ALN positive groups in invasive breast cancer.

Results

Eligible literatures

The searching deadline was Feb 12th, 2015. A total of 659 citations were identified from PubMed, 24 articles were remained after exclusion based on the titles and abstracts. 1 duplication, 3 original articles in Chinese language, 1 original article in Portuguese language, 5 articles that could not provide interested data, 5 articles in which cases were confided to special subjects and 3 original full texts that could not be obtained were removed. A total of 6 studies met the inclusion criteria for meta-analysis finally (**Figure 1**).

Characteristic of included studies

The final 6 studies were published from 2007 to 2014 and appraised critically (**Table 1**). In the studies of *[Rakha EA 2012] and [Gujam FJ 2014]* the cases were divided into three classifications according to tumor size: T≤1 cm, T>1-2 cm, T=2-5 cm and T≤2 cm, T=2-5 cm, T≥5 cm respectively, while the cases were combined into two classifications in this analysis correspondingly: T≤2 cm and T>2 cm. In the study of [*Aitken E 2010]* and *[Rakha EA 2012]* the cases were divided into three classifications according to the status of ALN: ALN negative; 1-3 ALN positive and no less than 4 ALN positive, while the cases were combined into two classifications in this analysis correspondingly: ALN negative and ALN positive. In the study of *[Lee JA 2011]* the cases were divided into two classifications: age <50 y and age ≥50 y according to age, but the two classifications were modified or combined into age ≤50 y and age >50 y in this analysis. It was unknown how many cases with just 50 y were in the article, the modification maybe affect the result very little. In the study of *[Lee JA 2011], [Rakha EA 2012] and [Gujam FJ 2014]* the cases were divided into three classifications according to histological grade: 1, 2 and 3. The latter two classifications were combined into one classification in this analysis, that was grade 2/3.

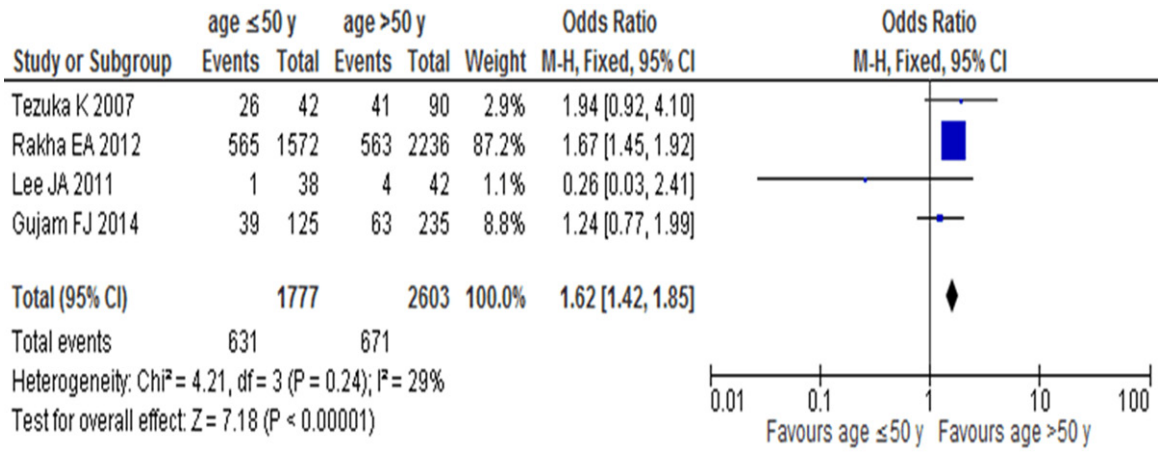

Figure 4. LVI positive rates between age ≤50 y and age >50 y groups in invasive breast cancer.

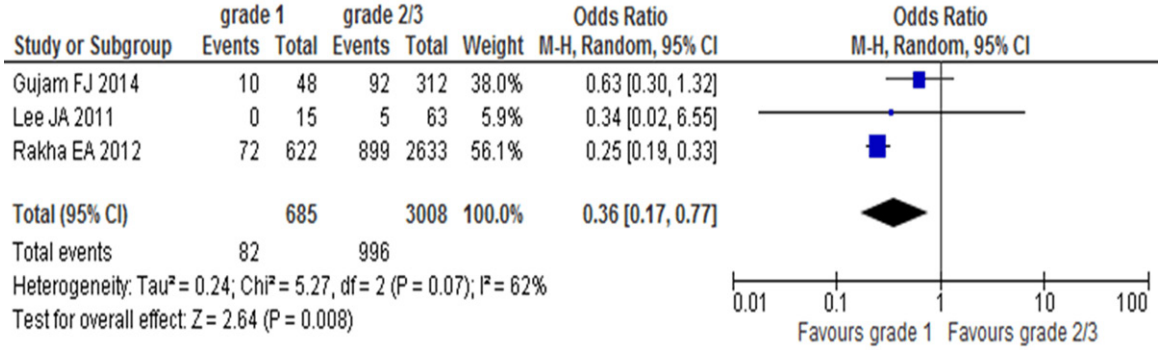

Figure 5. LVI positive rates between grade 1 and grade 2/3 groups in invasive breast cancer.

Correlation of LVI with the tumor size, status of ALN, age, histological grade in invasive breast cancer

LVI positive rates were compared between T≤2 cm and T>2 cm groups in invasive breast cancer in 4 studies. There was no significant heterogeneity (I^2=0, P=0.72). In the fixed-effect model there was statistical difference between T≤2 cm and T>2 cm groups (OR=0.50, 95% CI: 0.46-0.61, P<0.001) (**Figure 2**), which confirmed LVI positive rate was low in T≤2 cm group.

LVI positive rates were compared between ALN negative and ALN positive groups in invasive breast cancer in 6 studies. There was significant heterogeneity (I^2=87%, P<0.1), $N_{fs0.05}$= 1037.62, so random-effect model was adopted, there was statistical difference between ALN negative and ALN positive groups (OR= 0.23, 95% CI: 0.15-0.35, P<0.001) (**Figure 3**), which confirmed that LVI positive rate was low in ALN negative group.

LVI positive rates were compared between age ≤50 y and age >50 y groups in invasive breast cancer in 4 studies. There was no significant heterogeneity (I^2=29%, P=0.24). In the fixed-effect model there was statistical difference between age ≤50 y and age >50 y groups (OR=1.62, 95% CI: 1.42-1.85, P<0.001) (**Figure 4**), which suggested LVI positive rate was low in age >50 y group.

LVI positive rates were compared between grade 1 and grade 2/3 groups in invasive breast cancer in 3 studies. There was significant heterogeneity (I^2=62%, P=0.07). $N_{fs0.05}$=53.95, so random-effect model was adopted, there was statistical difference between grade 1 and grade 2/3 groups (OR=0.36, 95% CI: 0.17-0.77, P=0.008) (**Figure 5**), which suggested LVI positive rate was low in grade 1 group.

Evaluation of publication bias

As reports on LVI detected by H&E were rare in breast cancer, the publication bias was not

visualized by funnel plot due to fewer studies, but the fail-safe number could demonstrate that the publication bias may not exist.

Discussion

LVI is a crucial step in the complex process of tumor metastasis and an important criterion for further therapy. So it is a significant prognostic factor in invasive breast cancer with respect to local and distance recurrence [8] and poorer survival [11]. It is also associated with other strong prognostic factors including tumor size, grade and regional lymph node involvement [12].

The combined outcomes indicated that LVI was correlated with the tumor size, status of ALN, age, histological grade respectively in invasive breast cancer, and could act as a predictor of poor prognosis for invasive breast cancer.

In breast cancer, tumor size is powerful predictor for local recurrence, regional and systemic spread, therefore for OS. The individual OR value of the 4 studies ranged from 0.02 to 2.05, which indicated that the studies were not consistent about the relation between LVI and tumor size. But the meta-analysis confirmed LVI positive rate was significant lower in T≤2 cm group than that in T>2 cm group statistically (P<0.001).

The status of ALN is the most powerful prognostic factor for breast cancer patients to date. The prognosis of breast cancer patients with the ALN positive is poor. Because LVI increased the chances of the ALN positive, it was one of the predictors of the ALN positive [5]. The relations between LVI and ALN were consistent in included 5 studies except *[Lee JA 2011].* The individual OR value of the 5 studies ranged from 0 to 0.75, which indicated that the studies were consistent about the relation between LVI and ALN. [Rakha EA 2012] and [Lee JA 2011] were attributed to the high heterogeneity with the method of sensitivity analysis.The sample sizes in 2 studies were much bigger than those in the other 4 studies, so the high heterogeneity was ascribed to obvious difference of the sample sizes between the studies. The meta-analysis confirmed LVI positive rate was significant lower in ALN negative group than that in ALN positive group statistically (P<0.01). LVI offers an auxiliary method in the assessment of ALN status preoperatively, which may help the doctor in breast cancer counseling and decision-making for therapy.

A number of studies have demonstrated that younger age is a risk factor for ALN positive [5, 13]. This has been attributed to biologically more aggressive tumors in this younger age group [14]. The average age of menopause is about 50 y, so most literature set 50 y as cut-off point in exploring the relation between age and clinicopathological factors in invasive breast cancer. The individual OR value of the 4 studies ranged from 0.03 to 4.10, which indicated that the studies were not consistent about the relation between LVI and age. But the meta-analysis confirmed LVI positive rate was significant higher in age ≤50 y group than that in age >50 y group statistically (P=0.003).

LVI had correlation with histological grade. High grade and fast growing tumor may produce more growth factors and offer a bigger clonal variety of tumor cells capable of invading lymphatic vessels compared with low grade and slow growing tumor. The individual OR value of the 3 studies ranged from 0.02 to 1.32, which indicated that the studies were not consistent about the relation between LVI and histological grade. But the meta-analysis confirmed LVI positive rate was significant lower in grade 1 group than that in grade 2/3 group statistically (P=0.008). There was significant heterogeneity due to too few included studies and obvious difference of sample sizes between the studies.

In summary, LVI has unfavorable pathological features, and is significantly correlated with the tumor size, status of ALN, age, histological grade in invasive breast cancer. It was consistent with adverse features of the four factors, and showed an aggressive predictor. The method of LVI detected with H&E staining is easy and cheap in almost of all departments of pathology, thus it is considerable to list LVI as a marker of clinical typing for breast cancer. Moreover, anti-LVI therapy may become new therapeutic target for breast cancer.

Acknowledgements

We acknowledge the support of the directors and pathologists involved in the collection and analysis of the data in these individuals (Xin Xu, Kang-Sheng Bei, Ri-Chang Du, Gao-Fang Xiao).

Supported by National Natural Science Foundation of China No. 61427807; Fujian Province Introduction of Major Research and Development Institution Funding Project No. 2012I-2004.

Disclosure of conflict of interest

None.

Address correspondence to: Wen-Hua Huang, Department of Human Anatomy, Guangdong Provincial Key laboratory of Tissue Construction and Detection, School of Basic Medicine Science, Southern Medical University, 1023 South Shatai Road, Baiyun District, Guangzhou, P. R. China. Tel: +08613822232749; E-mail: huangwenhua2009@139.com

References

[1] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Schoppmann SF, Bayer G, Aumayr K, Taucher S, Geleff S, Rudas M, Kubista E, Hausmaninger H, Samonigg H, Gnant M, Jakesz R, Horvat R; Austrian Breast and Colorectal Cancer Study Group. Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. Ann Surg 2004; 240: 306-12.

[3] Vleugel MM, Bos R, van der Groep P, Greijer AE, Shvarts A, Stel HV, van der Wall E and van Diest PJ. Lack of lymphangiogenesis during breast carcinogenesis. J Clin Pathol 2004; 57: 746-751.

[4] Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ and Panel M. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16: 1569-1583.

[5] Aitken E and Osman M. Factors affecting nodal status in invasive breast cancer: a retrospective analysis of 623 patients. Breast J 2010; 16: 271-278.

[6] Gujam FJ, Going JJ, Mohammed ZM, Orange C, Edwards J and McMillan DC. Immunohistochemical detection improves the prognostic value of lymphatic and blood vessel invasion in primary ductal breast cancer. BMC Cancer 2014; 14: 676.

[7] Lee JA, Bae JW, Woo SU, Kim H and Kim CH. D2-40, Podoplanin, and CD31 as a Prognostic Predictor in Invasive Ductal Carcinomas of the Breast. J Breast Cancer 2011; 14: 104-111.

[8] Rakha EA, Martin S, Lee AH, Morgan D, Pharoah PD, Hodi Z, Macmillan D and Ellis IO. The prognostic significance of lymphovascular invasion in invasive breast carcinoma. Cancer 2012; 118: 3670-3680.

[9] Tezuka K, Onoda N, Takashima T, Takagaki K, Ishikawa T, Wakasa T, Wakasa K and Hirakawa K. Prognostic significance of lymphovascular invasion diagnosed by lymphatic endothelium immunostaining in breast cancer patients. Oncol Rep 2007; 17: 997-1003.

[10] Wu JL, Tseng HS, Yang LH, Wu HK, Kuo SJ, Chen ST and Chen DR. Prediction of axillary lymph node metastases in breast cancer patients based on pathologic information of the primary tumor. Med Sci Monit 2014; 20: 577-581.

[11] Lee AK, DeLellis RA, Silverman ML, Heatley GJ and Wolfe HJ. Prognostic significance of peritumoral lymphatic and blood vessel invasion in node-negative carcinoma of the breast. J Clin Oncol 1990; 8: 1457-1465.

[12] Lee AH, Pinder SE, Macmillan RD, Mitchell M, Ellis IO, Elston CW and Blamey RW. Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma. Eur J Cancer 2006; 42: 357-362.

[13] Gill PG, Luke CG and Roder DM. Clinical and pathological factors predictive of lymph node status in women with screen-detected breast cancer. Breast 2006; 15: 640-648.

[14] Rivadeneira DE, Simmons RM, Christos PJ, Hanna K, Daly JM and Osborne MP. Predictive factors associated with axillary lymph node metastases in T1a and T1b breast carcinomas: analysis in more than 900 patients. J Am Coll Surg 2000; 191: 1-6; discussion 6-8.