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Predictors of Sentinel Node Involvement in Breast Cancer

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ABSTRACT

Background: Sentinel lymph node biopsy has shown to be a good alternative procedure for axillary lymph node dissection and to lead to lower frequency of morbidity, though this technique has its own side effects. It needs especial equipment and may not be available in some medical centers, especially in developing countries. This study aimed to identify a subgroup of patients with higher probability of metastasis to sentinel lymph node that can be excluded from indications of this procedure.

Methods: In this cross-sectional study, the clinical data of 195 patients with breast cancer who underwent sentinel lymph node biopsy in Tehran, Iran, between 2009 and 2011 were reviewed. Whenever tumor features showed significant association with sentinel node metastasis in univariate analyses, logistic regression was used to identify independent predictors.

Results: Univariate analyses revealed that tumor size and lymphovascular invasion P <0.001, respectively). Moreover, age had an significant association with positive sentinel lymph node biopsy (SLNB) (P = 0.004). Other factors, including tumor grade, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor- 2, were not associated with positive sentinel lymph node biopsy in univariate analysis. All factors that showed significant association in univariate analysis remained statistically significant predictors of positive SLB in multivariate analysis.

Conclusions: It seems that young breast cancer patients, those who have tumors larger than 5 cm and those with lymphovascular invasion, are at an increased risk of sentinel lymph node metastasis.

Introduction

Breast cancer is the most common malignancy among women around the world.[1] In recent decades, major advances have been made in early diagnosis and treatment of breast cancer, but still it is among the leading causes of cancer-related deaths among women.[1]

The two main important predictors of survival in patients with breast cancer are lymph node metastasis and tumor size.[2] Lymph node status can help the clinician predict the risk of local recurrence and distant metastasis and therefore choose the right adjuvant therapy for the patients.[3] Axillary lymph node dissection (ALND) is commonly performed to investigate lymph node metastasis. In contrast to its benefits in guiding the treatment strategy, various complications are observed following this procedure,

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such as pain, numbness, limitation of arm movement, and lymphedema.[4-6]

Sentinel lymph node biopsy (SLNB) has been shown to be an alternative procedure to traditional ALND for evaluating lymph node status with low post-operative morbidity and high accuracy.[7] Previous studies comparing the complications of ALND and SLNB have shown that the latter leads to lower morbidity rates.[8-11] SLNB, which is now routinely performed in women with breast cancer, is an intervention that requires multiple equipment and co-operations of different departments. Different complications reported in the process of lymphatic mapping by methylene blue or isosulfan blue prove that there is a need to perform this procedure in only a selected subgroup of patients with a higher risk of SLN metastasis.[12,13]

Although SLNB is a safer procedure, it is not an absolutely safe technique and can lead -with a lower risk- to all potential complications which might be seen after ALND. In fact, SLNB has its own drawbacks and disadvantages in different aspects. For example, there are some reports emphasizing the complications related to blue dye injection. Methylene blue, which is used to determine the sentinel node, can results in skin discoloration and skin necrosis.[13,14] There are some reports of anaphylactic shock using isosulfan blue as vital dye to identify the SLN.[12,15-17] Moreover, Isosulfan blue can interfere with pulse oximetry leading to some problems in patient monitoring during the operation.[18] Furthermore, different pathological evaluations in the process of SLNB impose an economic burden on patients and the health care system and may prolong the duration of surgery.[19] In addition, SLNB needs some medications such as radionuclide drugs and equipment like gamma camera, so it would not be feasible for some medical centers to perform it, especially in developing countries and countries with limited resources.[20,21]

Considering these limitations, if we could identify the predictors of positive SLNB, indications of performing this procedure might need to be reconsidered in further research. This study was designed to assess the relationship between tumor pathological features and the SLNB results and to determine predictive factors of SLN metastasis.

Methods

This cross-sectional study was designed to demonstrate which tumor characteristics can predict SLN involvement in invasive breast cancer. A total of 195 patients with breast cancer who underwent SLNB in Tehran, Iran, between 2009 and 2011 were enrolled. The procedure had been performed by the same surgeon (the corresponding author) for all patients. The study was designed and conducted according to the latest Declaration of Helsinki for investigation on human subjects .

SLNB was performed by injecting blue dye alone, radioactive colloid alone, or a combination of both. Agent was injected in intradermal area of subareolar space for both palpable and non-palpable tumors. In cases that blue dye was used, SLN was detected as it stained blue after injection. In patients who were injected with radioactive agent, SLN was mapped using a Gamma probe (Europrobe II, Eurorad SA, France). The presence of tumor cells in SLN was assessed by intraoperative frozen section examination and if the results were negative, further investigation was done by hematoxylin and eosin (H&E) staining and immunohistochemical assay. The positive result from each of these three tests was considered as a positive SLN and further ALND was performed.

Patients were classified according to the results of SLNB (positive vs. negative). An electronic registry database (Hakim software, Pegahsoft Co.) was used to record patients' information. Clinicopathological features which were collected and compared between the two groups were age at the time of diagnosis, tumor size, histological grade, lymphovascular invasion, estrogen receptor (ER) and progesterone receptor (PR) expression, and human epidermal growth factor-2 (HER-2) status.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). Chi-square test was employed for comparison of age (< 40 and ≥ 40), tumor size, lymphovascular invasion, ER and PR expression, and HER-2 status between groups. Variables which showed significant association with positive SLN in univariate analysis were put into a logistic regression model in order to find independent predictors of positive SLN. For categorical variables, the first group was considered as the reference group in logistic regression. In all tests, P values < 0.05 were considered as statistically significant.

Results

A total of 195 patients were recruited, The mean age of the study participants was 47.36 ± 10.99 years (ranging from 26 to 80 years). 59 (30.3%) were younger than 40 years old and 136 (69.7%) were.

Lymphatic mapping, using blue dye alone, was performed in 83 (42.6%) patients radioactive agent alone in 6 (3.1%) patients, and the combined methodwas used for 96 (42.6%) patients (5.1% missing). The mean number of SLNs and axillary lymph nodes harvested and assessed for each patient were 1.76 ± 0.798 (ranging from 1 to 4) and 3.83 ± 5.74 (ranging from 0 to 21), respectively. SLNB was positive in 67 (34.4%) patients, and in 128 (65.6%) patients SLN was not involved by the tumor cells.

Univariate analysis revealed that tumor size and lymphovascular invasion in the primary tumor were significantly associated with a higher prevalence of

positive SLNB (P = 0.009 and P < 0.001, respectively). Patients younger than 40 years were more frequently diagnosed with a positive SLN (P = 0.004). Other factors including ER (P = 0.227), PR (P = 0.846), HER-2 (P = 0.210), and tumor grade (P = 0.126) were not predictors of positive SLN (Table 1).

In logistic regression, the strongest predictor of SLN involvement was tumor size larger than 5 cm (odds ratio = 7.520; 95% CI: 1.738–32.536). The second factor that showed to be a strong predictor was lymphovascular invasion with odds ratio of 3.988 (95% CI: 1.943–8.186), after controlling for age and tumor size. Results of logistic regression analyses are presented in table 2.

Discussion

In this cross-sectional study, we aimed to identify independent predictors of tumor metastasis to SLN. The clinical history of 195 patients who underwent SLNB was reviewed and tumor pathological features were compared between patients who had negative and positive SLN.

Table 1. Baseline characteristics of study participants

	Group 1	Group 2	P-value	OR (95% CI)
	Positive SLN total = 67	Negative SLN total = 128		
Age			0.004	
< 40	29 (43.3%)	30 (23.4%)		Referent
⩾ 40	38 (56.7%)	98 (76.6%)		0.401 (0.213 –0.755)
Agent injected			N/A*	N/A*
Blue dye	26 (38.8%)	57 (44.5%)		
Radioactive	3 (4.5%)	3 (2.3%)		
Combined	35 (52.2%)	61 (47.7%)		
Missing	3 (4.5%)	7 (5.5%)		
Tumor size			0.009	
⩽ 2	25 (37.3%)	60 (46.9%)		Referent
2–5	29 (43.3%)	58 (45.3%)		1.200 (0.629–2.288)
> 5	11 (16.4%)	5 (3.9%)		5.280 (1.663–16.767)
Missing	2 (3.0%)	5 (3.9%)		
Grade			0.126	
I	5 (7.5%)	21 (16.4%)		Referent
II	43 (64.2%)	64 (50.0%)		2.822 (0.988–8.057)
III	17 (25.4%)	34 (26.6%)		2.100 (0.674–6.539)
Missing	2 (3.0%)	9 (7.0%)		
ER			0.227	
Negative	11 (16.4%)	31 (24.2%)		Referent
Positive	49 (73.1%)	86 (67.2%)		1.606 (0.742–3.475)
Missing	7 (10.4%)	11 (8.6%)		
PR			0.846	
Negative	19 (28.4%)	36 (28.1%)		Referent
Positive	40 (59.7%)	81 (63.3%)		0.936 (0.478–1.833)
Missing	8 (11.9%)	11 (8.6%)		
HER-2			0.210	
Negative	36 (53.7%)	81 (63.3%)		Referent
Positive	23 (34.3%)	34 (26.6%)		1.522 (0.788–2.942)
Missing	8 (11.9%)	13 (10.2%)		
Lymphovascular invasion			< 0.001	
No	27 (40.3%)	84 (65.6%)		Referent
Yes	33 (49.3%)	26 (20.3%)		3.949 (2.016–7.736)
Missing	7 (10.4%)	18 (14.1%)		

** No statistical analysis was performed*
Abbreviations: ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor -2

Table 2. Predictors of SNL involvement using logistic regression

	P-value	Odds ratio	95% CI	
			Lower	upper
Age	0.043	0.487	0.232	0.976
Lymphovascular invasion	< 0.001	3.988	1.943	8.186
Tumor size (> 5 cm)	0.007	7.520	1.738	32.536

To our knowledge, few previous studies have assessed the predictors of SLN involvement. Yi *et al.* evaluated patients, who underwent SLNB, with primary diagnosis of ductal carcinoma in situ (DCIS) or microinvasive breast cancer (MIC). In univariate analysis, they reported an association between age and SLN involvement, but in logistic regression this association did not retain its significance.[22] Our results showed that, even after adjusting for other factors, age is an independent predictor. This can be a result of using different cutoff points for categorizing patients based on their age at the time of diagnosis (40 years in our study and 50 years in the study by Yi *et al.*). We used the mentioned cut-off point as it has been reported that patients younger than this age are at increased risk of axillary lymph node metastasis.[23] In addition, Other studies that focused on the predictors of SLN metastasis also found no association between age and SLN involvement.[24,25] It has been suggested that breast cancer arising in younger patients has a more invasive behavior, higher recurrence rate, increased risk of developing distant metastases, and poorer survival.[26-28]

Almost all previous studies have declared that presence of lymphovascular invasion in primary tumor can increase the chance of SLN involvement by tumor cells, which is consistent with our results.[22,24,25] In addition, different authors have claimed that lymphovascular invasion can increase the risk of non-sentinel axillary lymph nodes metastasis.[29,30] A tumor with the potential of invading lymphatic vessels easily spreads to lymph nodes that drain the tissue.

In the present study, another factor that was an independent predictor of SLN metastasis was tumor size. Tumors larger than 1.5 cm have been shown to be associated with positive SLNs in the study by Tan et al.[24] Yi *et al.* showed that tumor sizes between 2 and 5 cm are predictors of positive SLN in patients with primary diagnosis of microinvasive breast cancer (MIC) or ductal carcinoma in situ (DCIS).[22] However, the same result were not observed in patients with the final diagnosis of MIC or DCIS. In their study, a tumor larger than 5 cm had a significant association with a positive SLN, both in patients with primary and final diagnosis of MIC or DCIS. In another study conducted by Chen *et al.* Size was associated with SLN metastasis, although patients with tumor sizes larger than 4.5 cm were not enrolled in the study.[25] Our study did not support the idea that tumor size between 2 and 5 cm are associated with higher rates of SLN metastasis; however, the association was observed for tumors larger than 5 cm. Further studies would be recommended to determine an appropriate cut-off point for tumor size that best predicts involvement of SLN.

Additionally, factors that showed a strong association with SLN involvement in our study have been previously reported to be predictors of nonsentinel lymph node metastasis.[29-31]

In conclusion, our study revealed that patients younger than 40 years at diagnosis, with tumor sizes larger than 5 cm, and the presence of lymphovascular invasion in their primary tumors are at increased risk of being diagnosed as SLN positive. For these patients, we suggest that SLNB be skipped and that they undergo axillary. In this subgroup, SLNB seems not to have an added value in axillary staging, especially in the under-equipped centers where the procedure is not applied routinely and their patients are referred to the more advanced centers. Further research is necessary to assess cost-utility of SLNB in this subgroup of patients.

Conflict of interests

The authors have declared no conflicts of interest.

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