Predictive Factors of Axillary Lymph Node Metastasis in Breast Cancer

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Objective: *To identify clinical, radiologic and pathologic factors significantly related to axillary lymph node (ALN) metastasis in women with operable breast cancer.*
Material and Method: *Records of women with operable invasive breast cancer treated between July 2002 and May 2006 were reviewed. Data on the number of axillary nodes, number of positive nodes, preoperative clinical, mammographic, and pathologic characteristics of each breast cancer were retrieved. Multiple logistic regression analyses were used to identify significant predictors of ALN metastasis.*
Results: *Records of 590 patients were reviewed. Positive ALNs were found in 302 patients (51%). Independent and significant predictors of ALN metastasis included younger age, larger tumor size, presence of lymphovascular invasion, category 5 mammograms and low mammographic breast density. The combination of age less than 60 years, low mammographic breast density, category 5 mammogram, tumor larger 1 cm., and presence of lymphovascular invasion, had a specificity for predicting ALN metastasis of over 95%.*
Conclusion: *A combination of clinical, radiologic, and pathologic characteristics highly specific for predicting ALN metastasis was found. This prediction rule might be useful for selecting breast cancer patients for full ALN dissection without a preliminary SLNB.*

Keywords: *Axillary lymph node metastasis, Predictive factors*

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Knowledge of axillary lymph node (ALN) status is important for determining the prognosis and treatment of breast cancer. Surgical removal of the ALNs, whether partial or complete, is the most accurate method for evaluating the ALN status. However, surgical dissection of the axilla can lead to occasional debilitating complications, with increasing frequency for more extensive dissections[1,2]. It would be useful if the status of the ALNs can be determined without having to remove the lymph nodes surgically. In particular, certain characteristics of the patient and the primary cancer might be used to determine the lymph node status.

Many previous studies have found the accuracy of these predictive characteristics to be limited[3]. Nonetheless, in the era of the sentinel lymph node (SLN) biopsy, the scenario in which the knowledge of these characteristics might be of value is that of clinically node-negative breast cancer patients who have a high likelihood of ALN metastasis. If these characteristics can predict the presence of lymph node metastasis with great accuracy, then ALN dissection can be done without the need for a preliminary SLN biopsy[4]. That is, if certain combinations of patient and tumor characteristics are found to be very specific for ALN metastasis, then in patients with these characteristics, SLN biopsy can be omitted. The main objective of the present study was to determine such combinations of patient and tumor characteristics. Secondary objectives of the present study included the identification of factors associated with the number of positive lymph nodes, in particular, with the number of positive nodes of four or more[5,6].

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Material and Method

Medical records of women with operable invasive breast cancer treated between July 2002 and

May 2006 were reviewed. Although the authors began performing SLN biopsy in the year 2004, by 2006 less than 30% of patients underwent any form of SLN biopsy. The period under study therefore represented a time when routine ALN dissection was the rule. All patients with available data on ALN surgery were included in the present study, if they did not undergo SLN biopsy. The Hospital's Research Ethics Committee approved the present study.

Data on the number of axillary nodes removed and the number of nodes with breast cancer metastasis ("positive nodes") were abstracted. Other clinical, radiologic and pathologic data retrieved included: the age of the patients, mammographic breast density, BI-RADS (Breast Imaging Reporting and Data System) category, tumor size, histologic grading (Bloom-Richardson), and presence of lymphatic and vascular invasion. The estrogen (ER), progesterone (PR), and HER2 (human epidermal growth factors receptor-2) receptor expressions, which were assessed by means of histochemical techniques and graded from 1 to 3 as well as in terms of percentage of tumor cells expressed, were also obtained.

Continuous variables were summarized as mean (standard deviation) or median (range). Categorical variables were summarized as counts and percentage. The differences in the continuous variables between the two groups were tested using unpaired t-test or rank test, and the differences in categorical variables were tested using Chi-square or Fisher's exact test, as appropriate. Factors associated with the presence of positive axillary lymph nodes, or with the number of positive nodes greater than 3, were identified using multiple logistic regression analysis. Factors associated with number of positive lymph nodes, or the ratio of positive to total number of lymph nodes removed, were identified using quantile (robust) regression methods[7]. Statistical significance was defined as a two-sided p-value less than 0.05. All statistical analyses were performed using Stata version 9 (Stata Corp, College Station, TX, USA).

Results

Five hundred ninety medical records of female breast cancer patients were included in this study. The mean age of these patients was 52.0 years with a standard deviation of 11.3 years. Positive ALNs were found in 302 patients (51%). Other radiologic and pathologic characteristics are presented, as well as contrasted between node negative and node positive patients, in Table 1. A large number of patients had no reported measurements of hormonal receptor and HER2 expressions, because these measurements were not routine during the period under study.

On multivariable logistic regression analysis, only five factors were significantly associated with ALN metastasis after adjusting for total number of ALNs removed: younger age, lower mammographic density, higher BI-RADS category, larger tumor size, and presence of lymphovascular invasion (Table 2).

When only node-positive patients were considered, only two factors were associated with the number of positive ALNs at least four or more: larger tumor size and presence of lymphovascular invasion (Table 3).

Quantile (robust) regression with either the number of positive nodes as the outcome, or the ratio of positive to total number of nodes as the outcome, revealed that the only significant predictive factor was the presence of lymphovascular invasion.

Based on the model in Table 2, the area under the receiver operating characteristic curve, or the c-index, was 0.761. For the cutoff probability of positive ALN of 0.5, the sensitivity for predicting positive ALN was 70.2% with a 95% confidence interval (CI) between 64.7% and 75.3%, and the specificity was 68.8% with a 95 CI, 63.1% to 74.1%.

According to the data, the specificities of the probability cutoffs above 0.8 would have a median value of 98.6% with a range between 95.5% and 100%. One combination of values of factors that would give the cutoff probability of positive ALN of at least 0.8 was in a patient 60 years or younger, with a tumor size at least 1 cm in diameter, positive lymphovascular invasion, with BI-RADS category 5 mammogram, a breast of low mammographic density, and under the assumption that the total number of axillary lymph nodes to be removed would not be less than 10. A combination that would give cutoff probabilities greater than 0.9 and even higher specificities was in a patient aged less than 40 years, with a tumor larger than 2.5 cm, lympho-vascular invasion, BI-RADS category 5 mammogram, and breasts of low mammographic density.

Discussion

Predictive factors of ALN metastasis in the present study conformed to those found in most previous studies[3]. Age, tumor size and lymphovascular invasion have been consistently found to be associated with ALN metastasis[8]. Tumor cell expressions of ER, PR, and HER2 have not been consistent predictors of ALN metastasis[3,9] and in the present study, they were

Table 1. Characteristics of patients (n = 590)

Characteristic	ALN negative n = 288	ALN positive n = 302	p-value[a]
Age (years): mean (SD)	52.8 (10.9)	51.2 (11.7)	0.092
Mammographic breast density: number (%)			
Almost entirely fat	17 (6)	21 (7)	0.010
Fibroglandular density	73 (25)	112 (37)	
Heterogeneous density	190 (66)	165 (55)	
Extremely dense breast	8 (3)	4 (1)	
BI-RADS category: number (%)			
Category 3	1	2 (1)	<0.001
Category 4	149 (52)	70 (23)	
Category 5	138 (48)	230 (76)	
Size of mass lesion (cm.)			
Mean (SD)	2.4 (1.3)	3.3 (1.6)	<0.001
Median (range)	2 (0.5 to 9.5)	3 (0.5 to 10)	<0.001
Histological nuclear grade: number (%)			
I	42 (15)	18 (6)	<0.001
II	182 (63)	180 (60)	
III	64 (22)	104 (34)	
Lymphovascular invasion (yes): number (%)	56 (19)	147 (49)	<0.001
Total number of ALNs			
Mean (SD)	16.3 (5.7)	17.7 (7.0)	0.007
Median (range)	16 (5 to 38)	16 (5 to 43)	0.033
Number of positive nodes			
Mean (SD)	NA	6.3 (6.7)	NA
Median (range)	NA	4 (1 to 37)	
Ratio of positive nodes to total			
Mean (SD)	NA	0.34 (0.29)	NA
Median (range)			
ER expression (+): number (%)			
0 (negative)	112 (39)	123 (41)	0.006
1+	44 (15)	68 (23)	
2+	64 (22)	70 (23)	
3+	68 (24)	41 (14)	
Positive ER expression, % of tumor cells[b]			
Median (range)	80 (10 to 98); n = 46	80 (10 to 100); n = 31	0.614
PR expression (+): number (%); n = 425[b]			
0 (negative)	87/199 (44)	115/226 (51)	0.111
1+	34/199 (17)	35/226 (15)	
2+	35/199 (18)	46/226 (20)	
3+	43/199 (22)	30/226 (13)	
Positive PR expression, % of tumor cells[b]			
Median (range)	80 (25 to 100); n = 31	70 (10 to 95); n = 25	0.145
HER2 expression (+); number (%); n = 430[b]			
0 (negative)	145/202 (72)	142/228 (62)	0.159
1+ (negative)	5/202 (3)	11/228 (5)	
2+ (uncertain)	24/202 (12)	31/228 (14)	
3+ (positive)	28/202 (14)	44/228 (19)	

[a] p-value according to unpaired t-test, rank test, and Chi-square test as appropriate
[b] measures of ER, PR and HER2 expressions were not obtained for some patients
SD = standard deviation; ALN = axillary lymph node; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor-2; BI-RADS = breast imaging reporting and data system

Table 2. Multiple logistic regression analysis of factors associated with axillary lymph node metastasis, adjusted for total number of axillary nodes (n = 590)

Factor	Odds ratio (95% CI)	p-value
Age, per year increase	0.98 (0.96 to 0.99)	0.012
Dense vs. not dense breast[a]	0.51 (0.35 to 0.76)	0.001
BI-RADS categories 3 & 4 vs. category 5	2.64 (1.80 to 3.88)	<0.001
Tumor size, per cm. increase	1.31 (1.14 to 1.51)	<0.001
Lymphovascular invasion vs. none	2.99 (2.01 to 4.45)	<0.001

[a] Dense breast refers to mammographic density grades 3 and 4, *i.e.* heterogeneous and extremely dense breasts; not dense refers to grades 1 and 2, *i.e.* fatty and fibroglandular breasts

Table 3. Multiple logistic regression of factors associated with number of positive ALNs of four or more, adjusted for total number of axillary nodes (n = 302)

Factor	Odds ratio (95% CI)	p-value
Size of tumor, per cm. increase	1.42 (1.18 to 1.72)	<0.001
Lymphovascular invasion vs. none	2.03 (1.22 to 3.38)	0.006

not significant. Low mammographic breast density was found to be an independent predictor of ALN metastasis in the present study, although there was no clear biological reason why. In fact, some previous studies found no such association[(10)] and some found a converse association where low density was associated with a lower risk of ALN metastasis[(11)]. Selection bias might have explained the present finding.

Supplementary analyses revealed that factors related to the number of positive nodes of four or more were the size of the tumor and lymphovascular invasion, both associated with ALN metastasis as well. Similarly, the only factor associated with the number of nodal metastasis or the ratio of positive to total ALNs was lymphovascular invasion. This should underscore the special importance of the presence of lymphatic or vascular invasion in the tumor specimens for the prediction of ALN metastasis[(12)], and should therefore be routinely documented in all pathological examinations of breast cancers.

The overall accuracy of the prediction model presented in Table 2 was modest, with a c-index of only 0.761 and a sensitivity and specificity of 70.2% and 68.8%, respectively, at the nominal cutoff probability of 0.5. This was a common finding in almost all such predictive studies[(3)].

An example of the combination of characteristics found to be highly specific for the presence of ALN metastasis in the present study, *e.g.,* with a specificity of at least 96%, was in patients 60 years or younger with a tumor size at least 1 cm in diameter, with positive lymphovascular invasion, with BI-RADS category 5 mammogram, and a breast of low mammographic density.

A combination of characteristics highly specific for the prediction of ALN metastasis could be useful in several scenarios. As mentioned in the introduction, patients with values of factors or characteristics strongly predictive of the presence of ALN metastasis could be spared a SLN biopsy, so that a full ALN dissection could be performed at once. Patients undergoing neoadjuvant systemic therapy needing information on the cancer status of the axilla could also be spared a SLN biopsy if they have the right characteristics. By this means, the false negative SLN biopsy rate could be reduced as well.

Conversely, features strongly predictive of the absence of ALN metastasis might also be useful for certain patients. According to the data, for probability cutoffs below 0.2, the median sensitivity was 99% with a range between 97% and 100%. Patients with probabilities of ALN metastasis less than 0.2 included those with ages greater than 60 years, with tumor sizes smaller than 1 cm and no lymphovascular invasion, with higher mammographic breast densities and BI-RADS category 3 or 4 mammograms. Such patients might not require any form of ALN sampling or dissection. However, it might not be acceptable to do so, since missed ALN metastases are still possible, *i.e.*, due to a false negative prediction. This is especially relevant when the primary tumor has been biopsied using core needles.

The "prediction rules" mentioned above should be used to supplement the SLN-based strategies for evaluating the tumor status of ALNs[13]. Currently, there are no comprehensive prediction rules based on clinical, radiologic and primary tumor characteristics that can compete with the SLN-based ALN evaluation in terms of prediction accuracy or the extensiveness of external validation studies that have been done[3].

In actual practice, the utility of the results of the present study might be limited. Most breast tumors are now biopsied using core needles (gauge numbers 8 to 14) or fine needles (*e.g.,* gauge numbers 20 or 21). Fine needle biopsies cannot demonstrate and core needle biopsies sometimes miss areas with lymphovascular invasion. Therefore, the present study will be useful for patients who have undergone open biopsy or core needle biopsy. If a core needle biopsy is negative for lymphovascular invasion, the latter's presence cannot be ruled out, and a sentinel lymph node biopsy is indicated.

Methodological limitations of the present study included a large number of missing values for the hormonal and HER2 receptor expression measurements. However, this missing information might not affect the conclusions of the present study. Other clinical predictors, such as the location and multifocality of the cancer in the breast, were not obtained, but these might not be consistent predictors of ALN metastasis[3,14]. More recent possible markers and predictors of ALN metastasis were not measured in the present study[4,15], because they were not routinely obtained in clinical practice. Future studies should address these and other molecular-level predictors of ALN metastasis[16,17], including other radiologic approaches as well[4,18-20].

Conclusion

In the present study, significant factors predicting the presence of ALN metastasis in breast cancer included age, mammographic breast density, BI-RADS category, tumor size, and lymphovascular invasion. Combinations of values of these factors were found and were highly specific for the presence of ALN metastasis. Patients with these characteristics might be spared a SLN biopsy. External validation of this finding is needed to confirm the potential usefulness of the prediction rule.

Potential conflict of interest

None.

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ปัจจัยทำนายการพบมะเร็งกระจายไปต่อมน้ำเหลืองที่รักแร้ในผู้ป่วยมะเร็งเต้านม

ยอดยิ่ง วาสุถิตย์, เยาวนุช คงด่าน, รณรัฐ สุวิกะปกรณ์กุล, ภาณุวัฒน์ เลิศสิทธิชัย, ประกาศิต จิรัปปภา

วัตถุประสงค์*: เพื่อศึกษาปัจจัยทางคลินิก ทางรังสีวิทยา และทางพยาธิวิทยา ที่สามารถทำนายการพบมะเร็งกระจายไปต่อมน้ำเหลืองที่รักแร้ ในผู้ป่วยมะเร็งเต้านมที่ผ่าตัดได้*

วัสดุและวิธีการ*: ทบทวนข้อมูลจากเวชระเบียนของผู้ป่วยมะเร็งเต้านมที่ผ่าตัดได้ ที่มารับการรักษาที่โรงพยาบาลรามาธิบดี ระหว่างปี พ.ศ. 2547 ถึง พ.ศ. 2549 โดยศึกษาข้อมูลอันประกอบด้วย จำนวนต่อมน้ำเหลืองที่เลาะได้จำนวนต่อมน้ำเหลืองที่พบมะเร็งแพร่กระจาย ลักษณะทางคลินิกและรังสีวิทยาของก้อนมะเร็งที่เต้านมก่อนได้รับการผ่าตัด และข้อมูลทางพยาธิวิทยาหลังผ่าตัด ได้วิเคราะห์ข้อมูลโดยอาศัยตัวแบบถดถอยพหุคูณโลจิสติค*

ผลการศึกษา*: ได้ทบทวนข้อมูลจากผู้ป่วย 590 ราย พบมะเร็งในต่อมน้ำเหลืองที่รักแร้ 302 ราย คิดเป็นร้อยละ 51 กลุ่มปัจจัยที่เป็นอิสระต่อกัน ที่สามารถทำนายการพบมะเร็งที่ต่อมน้ำเหลืองดังกล่าว ประกอบด้วยอายุที่น้อย ก้อนมะเร็งขนาดใหญ่ การพบเซลล์มะเร็งลุกลามท่อน้ำเหลืองและหลอดเลือดในก้อนมะเร็ง การมีแมมโมแกรม BIRADS 5 และเนื้อเต้านมที่มีความหนาแน่นต่ำ และพบว่า การมีอายุน้อยกว่า 60 ปี มีเต้านมที่มีความหนาแน่นต่ำ มีแมมโมแกรม BIRADS 5 มีขนาดก้อนเนื้อเล็กกว่า 1 ซม. และพบการลุกลามท่อน้ำเหลืองและหลอดเลือดในก้อนมะเร็ง จะมีความจำเพาะในการทำนายว่ามีมะเร็งในต่อมน้ำเหลืองที่รักแร้ สูงกว่าร้อยละ 95*

สรุป*: การค้นพบกลุ่มปัจจัยที่มีความจำเพาะสูง ในการทำนายการพบมะเร็งกระจายไปยังต่อมน้ำเหลืองที่รักแร้ ในผู้ป่วยมะเร็งเต้านม อาจมีประโยชน์ในการเลือกผู้ป่วยเพื่อการเลาะต่อมน้ำเหลืองรักแร้แบบสมบูรณ์ โดยไม่ต้องเลาะต่อมน้ำเหลืองบางส่วนออกไปตรวจก่อน (sentinel lymph node biopsy)*