Research Paper

Use of CEA and CA15-3 to Predict Axillary Lymph Node Metastasis in Patients with Breast Cancer

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Abstract

Purpose: The clinical significance of preoperative serum levels of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) in breast cancer is controversial. The purpose of this study was to assess the clinical value of preoperative serum levels of CEA and CA 15-3 on the risk of axillary lymph node metastasis (ALNM) in patients with breast cancer.

Methods: This retrospective study analyzed 1148 breast cancer patients whose preoperative CEA and CA 15-3 levels were measured. The association of these tumor markers and clinico-pathologic parameters with ALNM was determined by univariate and multivariate analysis.

Results: A median of 15 lymph nodes were removed. Seven hundred seventy-eight (67.8%) patients had node-negative disease and 370 (32.2%) had ALNM. Univariate analysis showed that tumor location ($P = 0.024$), stage ($P = 0.001$), grade ($P < 0.001$), lymphovascular invasion (LVI) ($P < 0.001$), CEA level ($P < 0.001$), CA15-3 level ($P < 0.001$), and breast cancer subtype (BCS) ($P < 0.001$) were significantly associated with ALNM. ALNM was present in 4.5% of patients with normal CEA and 11.6% of patients with elevated CEA. ALNM was present in 8.0% of patients with normal CA15-3 and 17.0% of patients with high CA15-3. Multivariate logistic regression analysis showed that tumor location, stage, grade, LVI, CEA, CA15-3, and BCS were significantly and independently associated with ALNM ($P < 0.05$ for all).

Conclusion: The probability of ALNM was greater in patients with elevated preoperative serum levels of CEA and CA15-3. CEA and CA15-3 appear to be independent predictors of ALNM in breast cancer.

Key words: Breast cancer, axillary lymph node metastases, CEA, CA15-3.

Introduction

Axillary lymph node dissection (ALND) is an important procedure in the treatment of breast cancer because the results are used to predict patient prognosis and guide adjuvant therapy. However, complications of ALND can adversely affect patient quality-of-life (QOL) (1-3). An increasing number of pa-

tients experience these adverse effects because improvements in adjuvant therapy have improved survival rates. Therefore, it is very important to determine the effect of surgical procedures on the QOL of patients with breast cancer.

Numerous recent breast cancer studies have focused on the clinical significance of sentinel lymph node biopsy (SLNB). The results of the Z0011 trial showed that ALND did not affect the survival rate of patients with 0–3 positive sentinel nodes, and that sentinel lymph node biopsy can significantly improve patient QOL (4, 5). However, there is still controversy regarding the need for ALNB in patients with breast cancer. The 13th St. Gallen International Breast Cancer Conference (2013) only recommended SLNB for some patients in order to avoid ALND (6). Preoperative identification of axillary lymph node status is an important basis for selection of the most appropriate surgical procedure for the treatment of lymph nodes. However, there are currently no established standards. Therefore, a reliable and simple method is needed to predict the axillary lymph node status of patients with breast cancer.

Previous studies reported that 2 common markers of breast cancer, carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3), can predict patient prognosis (7-10). However, there have been no studies of the value of CEA and CA15-3 in predicting axillary lymph node status in patients with breast cancer. In the present study, we retrospectively analyzed the clinicopathologic factors and tumor markers of patients with breast cancer to determine whether CEA and CA15-3 can predict axillary lymph node status of these patients.

Patients and methods

Patients

The records of female patients with breast cancer who were admitted to the Sun Yat-Sen University Cancer Center (Guangzhou) between March 2001 and January 2007 were retrospectively reviewed. Each included patient had unilateral invasive breast cancer without distant metastasis at diagnosis, mastectomy or breast-conserving surgery and ALND, measurement of CEA and CA15-3 before surgery, complete surgical resection of the tumor and no residual tumor based on pathological exam, no neoadjuvant therapy before surgery, complete results of tests for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her 2), and no sign of malignant tumors in other organs at diagnosis.

Methods for measurement of CEA, CA15-3, and other pathological factors

Five mL of venous blood was collected from each patient upon admission. Serum was obtained after centrifugation, and was placed in a refrigerated tube and immediately preserved at -80°C.

Serum levels of CEA and CA15-3 were determined with the Roche E170 modular analytics immunoassay analyzer. We considered the normal range of CEA as 0–5 ng/mL and the normal range of CA15-3 as 0–25 U/mL. ER- and PR-positivity was defined by the presence of at least 1% positive cells based on immunohistochemical results. Her-2 positivity was defined as immunohistochemical grade of 3+ or 2+, as determined by fluorescence *in situ* hybridization (FISH). For measurement of Ki-67, the ratio of positive cells to total cells in a selected microscopic field was determined; "negative" was defined as less than 10% positivity, "weakly positive" as 10-25% positivity, "positive" as 26-50% positivity, and "strongly positive" as more than 50% positivity. Based on our previous studies, 25% positivity was used as the cut-off point (11).

Factors associated with axillary lymph node status

The axillary lymph node status was predicted using clinicopathologic and immunohistochemical factors including age, menopausal status, tumor location, tumor stage, grade, lymphovascular invasion (LVI), and breast cancer subtype (BCS). Tumor location was classified as outer (upper lateral and lower lateral) quadrant, inner (upper medial and lower medial) quadrant, and central. All cancers were categorized according to subtype: *(i)* ER+ and/or PR+, Her2+ (HR+/HER2-); *(ii)* ER+ and/or PR+, Her2+ (HR+/HER2+); *(iii)* ER-, PR-, and Her2+ (HR-/HER2+); or *(iv)* ER- and PR- and Her2- (HR-/HER2-).

Statistical analysis

All data were analyzed using the SPSS statistical software package (version 16.0; IBM, Armonk, NY, USA). The relationship between clinicopathologic factors, tumor markers, and ALNM was examined by univariate analysis using the χ^2 test and Fisher's exact test. Then multivariate logistic regression analysis was used, in which factors that were statistically significant in the univariate analysis were entered into multivariate logistic regression analysis. A *P*-value less than 0.05 was considered significant.

Results

Clinicopathologic status and lymph node re-section

A total of 1148 patients were retrospectively enrolled from March 2001 to January 2007 (Table 1). One thousand and seventy-six patients (93.7%) received mastectomy and 72 patients (6.3%) received breast conserving surgery. The median age was 47 years (range: 21–90 years). Serum CEA was elevated in 78 cases (6.8%) and serum CA15-3 was elevated in 125 cases (10.9%). Analysis of BCS indicated that 53.6% of patients had HR+/HER2- subtype, 16.2% had HR+/HER2+ subtype, 15.2% had HR-/HER2+ tumors, and 15.0% had HR-/HER2- (triple negative, TN) tumors. All patients underwent ALND. The median number of removed lymph nodes was 15 (range: 5–45). Overall, 778 patients (67.8%) had axillary node-negative disease and 370 patients (32.2%) had ALNM.

Table 1. Clinicopathologic characteristics of patients with breast cancer who presented with and without axillary lymph node metastases

Characteristics	N (%)	Lymph node negative (%)	Lymph node positive (%)	*p*-value
Age (year)				
≤ 35	140 (12.2)	92 (11.8)	48 (13.0)	0.579
> 35	1008 (87.8)	686 (88.2)	322 (87.0)	
Menopausal status				
Premenopausal	736 (64.1)	496 (63.8)	240 (64.9)	0.714
Postmenopausal	412 (35.9)	282 (36.2)	130 (35.1)	
Tumor location*				
Outer quadrant	725 (63.5)	475 (61.3)	250 (68.1)	0.024
Inner quadrant	278 (24.3)	207 (26.7)	71 (19.3)	
Central	139 (12.2)	93 (12.0)	46 (12.5)	
Tumor stage				
pT1	462 (40.2)	341 (43.8)	121 (32.7)	0.001
pT2	588 (51.2)	394 (50.6)	194 (52.4)	
pT3	59 (5.1)	28 (3.6)	31 (8.4)	
pT4	39 (3.4)	15 (2.0)	24 (6.5)	
Grade*				
I	118 (10.6)	102 (13.1)	16 (4.8)	< 0.001
II	523 (47.1)	375 (48.2)	148 (44.4)	
III	470 (42.3)	301 (38.7)	169 (50.8)	
Lymphovascular invasion				
Negative	1097 (95.6)	769 (98.8)	328 (88.6)	< 0.001
Positive	51 (4.4)	9 (1.2)	42 (11.6)	
CEA				
Normal	1070 (93.2)	743 (95.5)	327 (88.4)	< 0.001
High	78 (6.8)	35 (4.5)	43 (11.6)	
CA15-3				
Normal	1023 (89.1)	716 (92.0)	307 (83.0)	< 0.001
High	125 (10.9)	62 (8.0)	63 (17.0)	
Ki 67 (%)*				
≤ 25	447 (56.6)	316 (57.8)	131 (53.9)	0.312
> 25	343 (43.4)	231 (42.2)	112 (46.1)	
Breast cancer subtype				
HR+/HER2-	615 (53.6)	422 (54.2)	193 (52.2)	< 0.001
HR+/HER2+	186 (16.2)	107 (13.8)	79 (21.3)	
HR-/HER2+	175 (15.2)	114 (14.6)	61 (16.5)	
HR-/HER2-	172 (15.0)	135 (17.4)	37 (10.0)	

*With missing data.

Univariate analysis of risk factors with ALNM

Table 1 shows the results of univariate analysis of the correlation between clinicopathologic factors and ALNM. Tumor location (*p* = 0.024), tumor stage (*p* = 0.001), grade (*p* < 0.001), lymphovascular invasion (LVI) (*p* < 0.001), CEA (*P* < 0.001), CA15-3 (*p* < 0.001), and BCS (*p* < 0.001) were significantly associated with ALNM. Age, menopausal status, and Ki-67 were not associated with ALNM (*p* > 0.05 for all). A total of 4.5% of patients with normal CEA levels had ALNM, and 11.6% of those with high levels had ALNM. Similarly, a total of 8.0% of patients with normal CA15-3 levels had ALNM, and 17.0% of those with high levels had ALNM.

Multivariate analysis of risk factors with ALNM

Table 2 shows the results of multivariate logistic regression analysis of factors that were significant in the univariate analysis. Model 1 includes clinicopathologic factors, but not tumor markers. Model 2 includes the same clinicopathologic factors and tumor markers. In Model 1, tumor location, tumor stage, grade, LVI, and BCS were significant predictive factors for ALNM (*p* < 0.05 for all). In Model 2, all of these factors as well as CEA and CA15-3 levels were significantly and independently associated with ALNM (*p* < 0.05 for all). Patients with normal levels of CEA and CA15-3 had the lower risk for ALNM. Relative to patients with normal levels of CEA, those with high levels of CEA were significantly more likely to have ALNM (odds ratio [OR] = 2.139, 95% confidence interval [CI] = 1.261-3.630, *p* = 0.005). Relative to patients with normal levels of CA15-3, those with high levels of CA15-3 were significantly more likely to have ALNM (OR = 2.012, 95% CI = 1.321–3.064, *p* = 0.001).

Discussion

In the present study, we investigated the value of serum levels of CEA and CA15-3 in predicting ALNM in patients with breast cancer. Our results showed that elevated preoperative serum levels of CEA and CA-153 were significantly and independently associated with ALNM.

Axillary lymph node status is an important factor that affects the prognosis of breast cancer. Except for obtaining the results of pathological examination after SLNB or ALND, there is no definite standard to predict axillary lymph node status. Previous studies of patients with breast cancer reported that the risk factors for ALNM included age, tumor stage, BCS, tumor grade, and LVI (12-16). In the present study, we also found that tumor location, tumor stage, tumor grade, LVI, and BCS were independent factors predicting ALNM. However, no previous studies have

assessed the clinical value of CEA and CA15-3 in predicting ALNM in patients with breast cancer. Our previous studies indicated that serum levels of CEA and CA15-3 could be used to predict the survival of patients with breast cancer (7). The results of the present study suggest that CEA and CA15-3 can be used to predict ALNM as well as hematogenous metastasis of breast cancer.

Table 2. Multiple logistic regression analysis of the association of clinicopathologic characteristics with axillary lymph node metastases in patients with breast cancer.

Characteristics	HR	CI	*p*-value
Model 1			
Tumor location			
Inner quadrant vs. outer quadrant	0.635	0.450-0.896	0.010
Central vs. outer quadrant	0.825	0.535-1.272	0.383
Tumor stage			
pT2 vs. pT1	1.290	0.961-1.732	0.090
pT3 vs. pT1	2.586	1.405-4.762	0.002
pT4 vs. pT1	3.779	1.834-7.788	< 0.001
Grade			
II vs. I	2.266	1.258-4.085	0.006
III vs. I	3.456	1.925-6.206	< 0.001
Lymphovascular invasion			
Positive vs. negative	9.434	4.430-20.093	< 0.001
Breast cancer subtype			
HR+/HER2- vs. HR-/HER2-	1.258	0.819-1.931	0.294
HR+/HER2+ vs. HR-/HER2-	1.869	1.133-3.084	0.014
HR-/HER2+ vs. HR-/HER2-	1.640	0.986-2.729	0.057
Model 2			
Tumor location			
Inner quadrant vs. outer quadrant	0.626	0.443-0.885	0.008
Central vs. outer quadrant	0.818	0.529-1.265	0.366
Tumor stage			
pT2 vs. pT1	1.321	0.984-1.775	0.064
pT3 vs. pT1	2.530	1.365-4.691	0.003
pT4 vs. pT1	3.143	1.494-6.612	0.003
Grade			
II vs. I	2.192	1.225-3.922	0.008
III vs. I	3.482	1.949-6.220	< 0.001
Lymphovascular invasion			
Positive vs. negative	10.061	4.679-21.632	< 0.001
CEA			
High vs. normal	2.139	1.261-3.630	0.005
CA15-3			
High vs. normal	2.012	1.321-3.064	0.001
Breast cancer subtype			
HR+/HER2- vs. HR-/HER2-	1.283	0.832-1.979	0.259
HR+/HER2+ vs. HR-/HER2-	1.790	1.077-2.974	0.025
HR-/HER2+ vs. HR-/HER2-	1.522	0.904-2.563	0.114

At present, the molecular mechanism underlying the association of CEA and CA15-3 with ALNM is unknown. Previous research reported that adhesion molecules play a key role in tumor invasion of the lymphatic lumen (17), and that CEA may act as a cell adhesion molecule during tumor invasion (18). CA15-3 is a member of the mucin-1 (MUC-1) family of glycoproteins. MUC-1 expression has tissue specificity, and is mainly expressed in the epithelial tissue of the normal and cancerous mammary glands, but not in the mesenchyme-derived lymph nodes (19, 20). This may explain the positive association of serum levels of CEA and CA15-3 with ALNM in our patients. In agreement, Kim et al. measured the concentrations of CA-15-3 and CEA in fine-needle aspirates of axillary lymph nodes and found that their concentrations could be useful for pre-surgical diagnosis of ALNM in patients with breast cancer (21).

Previous studies indicated that ALNM was less common in patients with TN breast cancer than in those with other BCS (12, 16). In the present study, we also found that ALNM was less common in patients with TN breast cancer than in those who were HR+/HER2+. Our previous studies also showed that CEA levels were lower in patients with TN breast cancer than in those with other subtypes (*p* = 0.002) (7). Taken together, these findings suggest that TN breast cancer has unique biological behaviors.

At present, there is controversy regarding the use of CEA and CA15-3 in the diagnosis of breast cancer. The European Society for Medical Oncology (ESMO) and the European Group on Tumor Markers (EGTM) suggested that routine measurement of tumor markers such as CEA and CA15-3 should be performed in patients with breast cancer (22, 23). However, the American Society of Clinical Oncology (ASCO) does not recommend routine measurement of CEA, CA15-3, or other tumor markers for patients with breast cancer (24). A report that used Surveillance, Epidemiology and End Results (SEER) records (39,650 patients) suggested that tumor markers (including CEA and CA153) should not be routinely measured in patients with early-stage breast cancer. However, this study only enrolled patients who were at least 65 years-old (25). Although there have not yet been randomized controlled trials, the results presented here and additional studies support the use of CEA and CA15-3 for prediction of the prognosis of breast cancer (7-10). More generally, routine measurement of tumor markers can be helpful for predicting the prognosis and the axillary lymph node status of breast cancer patients.

SLNB is appropriate for some early-stage breast cancers, and the results can predict axillary lymph node status and help to determine whether ALND is necessary. Most patients in the present study had total mastectomy with ALND, and both were outside the Z0011 selection criteria (*i.e.* patients who need ALND). However, based on our study, we believe that detailed evaluation of axillary lymph node status is necessary for CEA- and CA15-3-positive patients during SLNB before surgery.

The present study had some limitation. This was a single-center retrospective analysis, and this may

have biased the results. Our findings may not be applicable to other populations. Second, SLNBs were not performed in our patients, so we do not know whether serum levels of CEA and CA15-3 can be used to predict the sentinel lymph node status in patients with breast cancer.

Conclusion

In conclusion, the results of the present study show that patients with breast cancer who test positive for CEA and CA15-3 before surgery have increased risk of ALNM. Therefore, clinicians should consider the use of preoperative serum levels of CEA and CA15-3 for guiding locoregional management decisions if further confirmed in larger sample size studies.

Abbreviations

ALND, axillary lymph node dissection; QOL, quality-of-life; SLNB, sentinel lymph node biopsy; CEA, carcinoembryonic antigen; CA15-3, cancer antigen 15-3; ER, estrogen receptor; PR, progesterone receptor; Her 2, human epidermal growth factor receptor 2; FISH, fluorescence *in situ* hybridization; LVI, lymphovascular invasion; BSC, breast cancer subtype; TN, triple negative; OR, odds ratio; CI, confidence interval; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; SEER, Surveillance, Epidemiology and End Results.

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Conflict of interest

No any actual or potential conflicts of interest exist.

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