

RESEARCH COMMUNICATION

Does the Pre-operative Value of Serum CA15-3 Correlate with Survival in Breast Cancer?

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Abstract

Introduction: CA15-3 is a well-known tumour marker for breast cancer. Currently it is not recommended for screening or diagnosis of breast cancer and its main application is in monitoring response to treatment in women with metastatic breast cancer. The aim of this study was to correlate serum CA15-3 at presentation with the stage of disease and overall survival in women with breast cancer in the University Malaya Medical Centre. **Methods:** This is a retrospective study of 437 women who had CA15-3 levels determined at initial presentation of breast cancer to UMMC between Jan 1999 and Oct 2003. **Results:** Of those patients who were adequately staged, CA15-3 was found to be elevated (defined as >51 U/ml) in 0% of Stage 1, 7.9% of Stage 2, 36.7% of Stage 3 and 68.6% of Stage 4 cases. In a subset of 331 patients with survival data, patients with normal CA15-3 had a 85% five year overall survival rate compared to 38% in their counterparts with elevation of the tumor marker. The level of elevation was also significantly related to survival; patients with values more than 200 U/ml exhibited only a 28% five year survival. The association of elevated CA15-3 at initial presentation with poor outcome was maintained over univariate and multivariate analyses. **Conclusion:** Estimation of CA15-3 at presentation of breast cancer is important as it is an independent prognostic indicator and may prompt the physician to investigate for metastases if elevated.

Key Words: CA15-3 - breast cancer - survival - prognostic marker

Asian Pacific J Cancer Prev, 9, 445-448

Introduction

Serum CA15-3 has been extensively investigated for the past two decades as a tumor marker for breast cancer. Elevated CA 15-3 levels correlate with higher stage, larger tumor size, lymph node spread and metastatic disease. Current evidence does not recommend the routine use of CA15-3 as a screening or diagnostic tool because of its low sensitivity (15-35%) in early breast cancer (Bast et al., 2001). Its main uses are in the surveillance of patients with diagnosed disease and monitoring the treatment of patients with advanced disease. Recent advances in genomic profiling and biochemical markers have identified numerous prognostic and predictive markers that may revolutionize the management of breast cancer. As genetic research is still in the stage of infancy in Malaysia, only routine clinicopathological staging and histopathological markers e.g. grade, ER receptors, PR receptors and HER2 are the main factors used in prognosticating patients. Serum CA 15-3 is cheap and easily available in Malaysia and its role as prognostic marker has yet to be determined. Raised levels of serum CA15-3 were shown to be associated with early relapse and death (Shering et al., 1998; Ebeling et al., 1999; Ebeling et al., 2002). The aim of this study is to correlate

preoperative serum CA15-3 with overall survival in breast cancer patients in the University Malaya Medical Centre and to assess the potential use as a prognostic marker

Materials and Methods

This analysis is a retrospective review of 437 women with breast cancer in the University Malaya Medical Centre from January 1999 to October 2003. Only patients with confirmed and untreated primary breast cancer and had serum CA15-3 taken before and within 2 weeks of surgery were included. Levels above 51 U/ml were abnormal. The AJCC Clinical Staging system was used to stage the cancer and the Bloom and Richardson Grading system was used in the grading of the tumours.

Mortality data were obtained from the National Registry of Malaysia. Survival data was censored after 60 months and excluded patients who survived beyond 60 months. The final complete data set was a review of 331 women.

Results

In the 322 patients who were fully staged and had CA15-3 estimated, the majority were Stage 2 (43.2%).

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No patient with Stage 0 and Stage 1 disease had elevated CA15-3 levels (0 %) compared to the high percentage of patients with elevated CA15-3 in Stage 4 (68.6%). Only 11 patients (7.9%) of 139 patients in Stage 2 disease had elevated markers while. 36.7% of Stage 3 patients had elevated tumour markers (Figure 1). Overall, only 68 patients of the 322 patients (21.1%) with breast cancer had elevated CA15-3 . The relationship between elevated CA15-3 and clinical stage was found to be statistically significant. (p<0.001).

In the survival data subset of 331 patients, 78 patients (23.6%) succumbed to the disease. In this subset, 64 patients had elevated CA15-3 levels, in which 41 (64.1%) died, as compared to only 13.9% of patients with normal values. Patients with normal CA15-3 have a 85% five year overall survival rate compared to 38% five year survival rate in patients with elevated CA15-3 (Figure 2). Using log rank analysis, overall survival correlated with tumor marker positivity (p < 0.0001).

Actual values of CA15-3 were analyzed to assess its prognostic value. CA15-3 levels were further subdivided into 4 categories: <50, 50-99, 100-199 and >200 U/ml. Univariate and log rank survival analysis found statistical significance (p< 0.0001) when comparing survival in patients with different values. Patients with values more than 200 U/ml have a 28% five year survival compared to 85% five year survival in patients with normal values (Figure 3).

CA 15-3 marker was then compared with other prognostic markers in a univariate analysis and tumour grade, size, and nodal status, together with CA15-3 were found to be markers for poorer outcome (Table 1). On multivariate analysis (Table 2), CA15-3 retained its prognostic value.

Discussion

The American Society of Clinical Oncologists (ASCO) recommendation for the use of CA15-3 in breast cancer

Table 1. Comparative Prognostic Factors for Overall Survival - Univariate Analysis

Characteristic	Comparison	Hazard Ratio	CI 95%	P value
CA 15-3	Pos vs. Neg	6.2	3.9-9.7	<0.0001
Tumor Size	T4 vs. T1	10.9	5.0-24.1	<0.0001
	T3 vs. T1	7.2	2.9-17.8	<0.0001
	T2 vs. T1	3.8	1.7-8.4	<0.0001
Nodal Stage	N3 vs. N0	4.7	2.7-8.2	<0.0001
	N2 vs. N0	2.0	1.0-3.9	<0.0001
Histological Grade	G3 vs. G1	5.4	1.3-22.0	0.0011
	G2 vs. G1	2.7	0.6-11.3	0.0011
ER status	Neg vs. Pos	0.4	0.2-0.6	<0.0001

Table 2. Comparative Prognostic Factors for Overall Survival - Multivariate Analysis

Characteristic	Comparison	Hazard Ratio	CI 95%	P value
CA 15-3	Pos vs. Neg	5.7	2.6-12.3	<0.0001
Nodal Stage	N3 vs. N0	7.9	3.5-18.1	<0.0001
Histological Grade	G3 vs. G1	2.6	1.3-5.7	0.0011

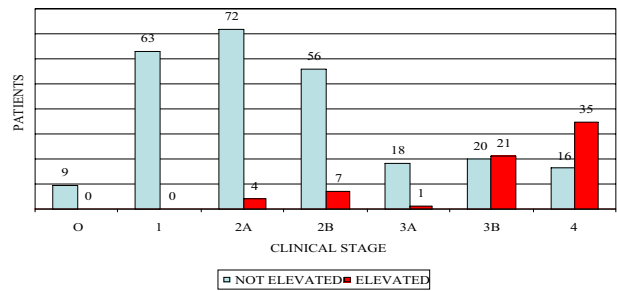


Figure 1. Correlation of CA15-3 Elevation and Clinical Stage

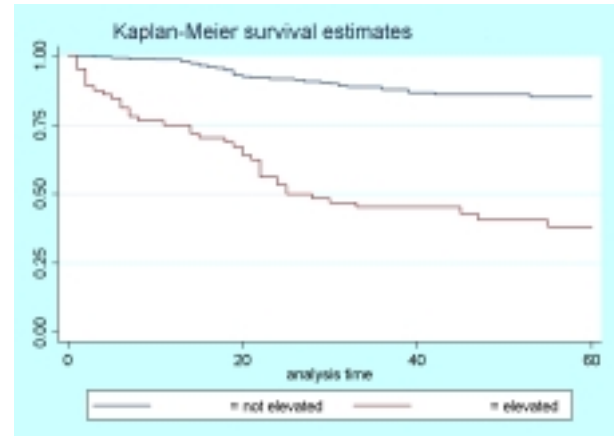


Figure 2. Kaplan Meier Survival Estimates, with reference to CA 15-3

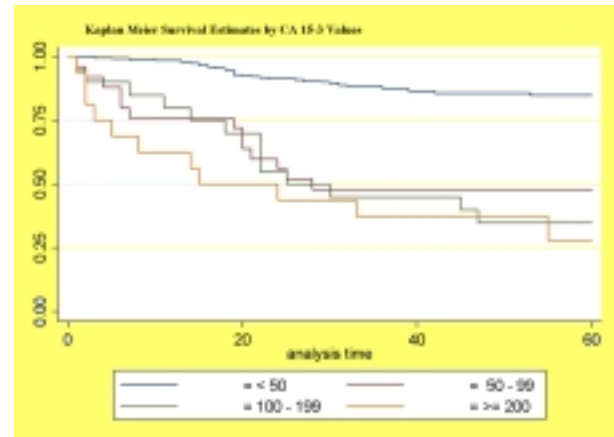


Figure 3. Survival Estimates by CA15-3 values

is that CA15-3 can be used for monitoring patients with metastatic disease during active therapy. CA15-3 can be used in conjunction with diagnostic imaging, history, and physical examination; however present data are insufficient to recommend use of CA15-3 alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA15-3 may be used to indicate treatment failure. CA15-3 is not recommended for screening, diagnosis or staging for breast cancer, or for detecting recurrence (Bast et al., 2001; Duffy, 2006).

This study demonstrated a correlation between stage of breast cancer and CA15-3 positivity rates. The higher the stage, the more likely that CA15-3 will be elevated. The low incidence of CA15-3 elevation in early stage disease indicates that it cannot be used in screening or diagnosis. Even in patients with breast cancer, CA15-3

was normal in up to 40% and 30% of patients with Stage 3 and 4 respectively. A normal result does not prove absence of tumor (Bast et al., 2001). This study is comparable with results from various analyses regarding CA15-3 and tumor stage (Kerin et al., 1989; Gion et al., 1991; O'Hanlon et al., 1995)

The potential use of CA15-3 as a prognostic marker in our center was then analyzed. Serum CA15-3 assay would be an ideal prognostic tool in our community because of the ease of sampling, availability and cost. Several studies have been carried out to address the relationship between CA15-3 levels and patient outcome, and the majority have shown that high preoperative levels of CA15-3 is associated with an adverse patient outcome (Shering et al., 1998; Ebeling et al., 1999; Duffy et al., 2000; Ebeling et al., 2002; Kumpulainen et al., 2002; Duffy et al., 2004). In some studies, the prognostic impact of CA15-3 was independent of tumor size and axillary nodal status (Shering et al., 1998; Kumpulainen et al., 2002; Duffy et al., 2004). The present study confirmed that high preoperative levels of CA15-3 were associated with poorer survival in both univariate and multivariate analyses. Canizares et al. however found that in multivariate analysis, only node status, DNA ploidy and ornithine decarboxylase activity were independent predictors for relapse-free survival; the estrogen receptor status was a predictor of overall survival, and CA15-3 was not a predictor of outcome in multivariate analyses (Canizares et al., 2001).

Berutti et al. evaluated the prognostic significance CA 15-3 in breast cancer patients at first recurrence of disease, and found that survival in this group of patients with recurrence significantly higher in women with lower CA15-3 levels (Berutti et al., 1994). However Tampellini et al., although confirmed the positive prognostic influence of a low CA15-3 serum levels in a univariate survival analysis, found in a multivariate Cox's survival analysis that disease extent in liver, lung, bone and soft tissue but not level of CA15-3 were poor prognostic factors. He concluded that CA15-3 is not an independent variable in determining survival in metastatic disease, its prognostic role being linked to the disease extent. This association suggests that CA15-3 may be useful in assessing disease extent when this is not easily assessable (Tampellini et al., 1997).

Monitoring serum CA15-3 levels during first-line chemotherapy or hormone therapy in advanced breast cancer patients could provide prognostic information independently from tumor response. A significant relationship was found between disease response and CA15-3 level (Bartsch et al., 2006; Tampellini et al., 2006). In this study, besides demonstrating that an elevated of CA15-3 was important in the prognosis, the level of elevation was important. The higher the levels, the poorer the prognosis. However how much the higher levels correlate to a greater extent of disease is not clear. Survival may be poorer in patients with elevated CA15-3 because of the statistical significant relationship between CA15-3 and clinical stage.

CA15-3, by itself, has not been shown to be a more useful prognostic marker than the routine

histopathological markers like tumor size, nodal stage, grade and stage. However, it may be used collectively with these markers in the management of breast cancer. A raised CA15-3 may prompt the physician to exclude the presence of metastatic disease. Hence an initial estimation of CA15-3 should be a routine investigation in the management of a patient with breast cancer.

The major limitation of this study is that it is a retrospective review with a small study population. The small number of patients in Stage 3 and 4 may not demonstrate serum CA15-3 as an independent prognostic factor.

Although current research interest internationally focuses on developing new proliferative and genomic markers, in Malaysia this field of research is in early stages. Furthermore there are many more aspects of breast cancer management that needs to be expanded e.g. screening programmes, mammogram services and providing quality adjuvant and palliative care. However the aim is to provide the best services possible despite the limitations and constraints and hope to provide future data and research on prognostic markers in breast cancer. Hence estimation of CA15-3 should be a routine investigation in the management of breast cancer.

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