RESEARCH ARTICLE

Prognostic Value of Preoperative Serum CA 242 in Esophageal Squamous Cell Carcinoma Cases

Ji-Feng Feng[1], Ying Huang[2], Qi-Xun Chen[1]*

Abstract

Purpose: Carbohydrate antigen (CA) 242 is inversely related to prognosis in many cancers. However, few data regarding CA 242 in esophageal cancer (EC) are available. The aim of this study was to determine the prognostic value of CA 242 and propose an optimum cut-off point in predicting survival difference in patients with esophageal squamous cell carcinoma (ESCC). Methods: A retrospective analysis was conducted of 192 cases. A receiver operating characteristic (ROC) curve for survival prediction was plotted to verify the optimum cuf-off point. Univariate and multivariate analyses were performed to evaluate prognostic parameters for survival. Results: The positive rate for CA 242 was 7.3% (14/192). The ROC curve for survival prediction gave an optimum cut-off of 2.15 (U/ml). Patients with CA 242 ≤ 2.15 U/ml had significantly better 5-year survival than patients with CA 242 >2.15 U/ml (45.4% versus 22.6%; *P*=0.003). Multivariate analysis showed that differentiation (*P*=0.033), CA 242 (*P*=0.017), T grade (*P*=0.004) and N staging (*P*<0.001) were independent prognostic factors. Conclusions: Preoperative CA 242 is a predictive factor for long-term survival in ESCC, especially in nodal-negative patients. We conclude that 2.15 U/ml may be the optimum cuf-off point for CA 242 in predicting survival in ESCC.

Keywords: Esophageal cancer - squamous cell carcinoma - CA 242 - tumor marker - prognostic factor - survival

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Introduction

Esophageal cancer (EC) is the 8th most common cancer worldwide, with 482,000 new cases in 2008, and the 6th most common cause of death from cancer, with 406,000 deaths (Ferlay et al., 2010). According to the GLOBOCAN project in 2008, China was estimated to account for 53.6% of the new cases and 51.7% of the deaths worldwide respectively (Ferlay et al., 2010). Thus, China still suffers a great disease burden from EC. Although advances have occurred in the multidisciplinary treatment, surgical resection remains the modality of choice. The overall 5-year survival after surgical resection is poor, the reason of that is the relatively late stage of diagnosis and rapid clinical progression (Lerut et al., 1994; Ferguson et al., 1997; Mao et al., 2011; Mirinezhad et al., 2012). Therefore, assessing the prognostic factors in EC patients will become more and more important.

Serum tumor markers play an important role in cancer diagnosis, prognosis, treatment and monitoring (Chen et al., 2004; Jiang et al., 2012). Thus, in order to further improve the survival rate of EC patients, it is essential to explore and identify relevant biomarkers with adverse prognosis. Recent publications have suggested that CA 242 is inversely related to prognosis in many cancers, high CA 242 is associated with poor prognosis (Kuusela et al., 1991; Bünger et al., 2011; Rana et al., 2012).

However, to date, few data regarding CA 242 in EC are available. The aim of this study was to determine the prognostic value of CA 242 and propose the optimum cut-off point for CA 242 in predicting survival difference in patients with esophageal squamous cell carcinoma (ESCC).

Materials and Methods

Patients

A retrospective analysis was conducted of 192 patients with ESCC who underwent curative esophagectomy at the Department of Thoracic Surgery, Zhejiang Cancer Hospital (Hangzhou, China) from January 2006 to December 2007. The inclusion criteria were as follows: (1) ESCC was confirmed by histopathology; (2) curative esophagectomy with R0 resection; (3) at least six lymph nodes were examined for pathological diagnosis; (4) surgical resection was neither preceded nor followed by adjuvant chemotherapy and/or radiotherapy; and (5) serum CA 242 were obtained before esophagectomy. All the subjects gave written informed consent to the study protocol, which was approved by the Ethical Committees of Zhejiang Cancer Hospital, Hangzhou, China. The last follow-up was 30 November 2011.

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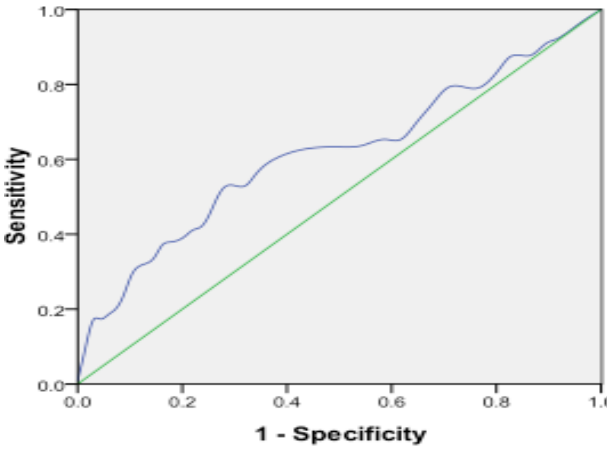

Figure 1. A ROC Curve for Survival Prediction was Plotted to Verify the Optimum Cuf-off Point for CA 242, Which was 2.15 U/ml. The area under curve (AUC) for CA 242 was 61.4% (95% CI: 0.534-0.694) with a sensitivity of 52.4% and a specificity of 72.1% (*P*=0.009)

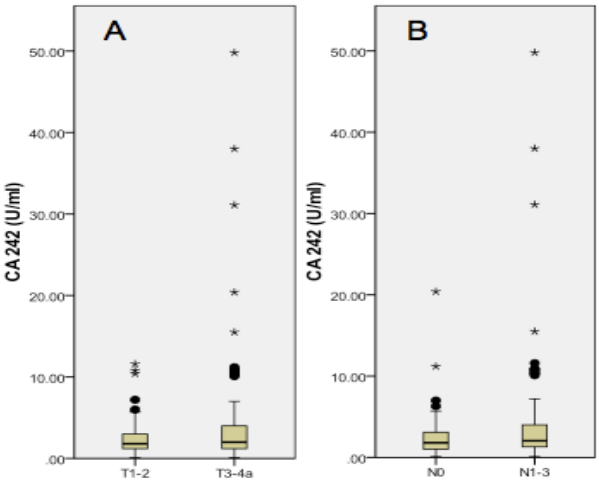

Figure 2. CA 242 were Significantly Higher in Patients with Deeply Invasive Tumors (T3-4a versus T1-2; P=0.037) (A) and node involvement (N1-3 versus N0; *P*=0.029) (B)

Table 1. The Baseline Characteristics for Patients with CA 242 ≤ 2.15 U/ml and >2.15 U/ml

	CA242 ≤ 2.15 U/ml (n, %)	CA242 > 2.15 U/ml (n, %)	*P*-value
Age (years)			0.73
≤60	72 (66.7)	54 (64.3)	
>60	36 (33.3)	30 (35.7)	
Gender			0.606
Female	17 (15.7)	11 (13.1)	
Male	91 (84.3)	73 (86.9)	
Tumor length (cm)			0.368
≤3.0	32 (29.6)	20 (23.8)	
>3.0	76 (70.4)	64 (76.2)	
Tumor location			0.826
Upper/Middle	60 (55.6)	48 (57.1)	
Lower	48 (44.4)	36 (42.9)	
Differentiation			0.174
Well/Moderate	94 (87.0)	67 (79.8)	
Poor	14 (13.0)	17 (20.2)	
T grade			0.135
T1-2	42 (38.9)	24 (28.6)	
T3-4a	66 (61.1)	60 (71.4)	
N staging			0.443
N0	51 (47.2)	35 (41.7)	
N1-3	57 (52.8)	49 (58.3)	

Surgery

The left transthoracic procedure and Ivor-Lewis procedure with anastomosis of the upper chest were performed for all tumors of the lower thoracic esophagus and some tumors of the middle thoracic esophagus. The McKeown procedure was used for all tumors of the upper thoracic esophagus and some tumors of the middle thoracic esophagus. In our institute, the majority of patients underwent two-field lymphadenectomy. All of the patients included in the study were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (Rice et al., 2010).

CA 242 analysis

The peripheral blood was obtained at the preoperative workup. And the serum was separated and stored at -20ºC until detection using the C12 protein chip system according to the protocol supplied by the manufacturer (Shanghai Health Digit Co., Ltd. Shanghai, China). The cut-off value for CA 242 was 10 U/ml.

Statistical analysis

Statistical evaluation was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). A receiver operating characteristic (ROC) curve for survival prediction was plotted to verify the optimum cuf-off point for CA242. The area under curve (AUC) was used as an estimation of diagnostic accuracy. The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and the difference was assessed by the log-rank test. Univariate and multivariate analyses of Cox regression proportional hazard model were performed to evaluate the prognostic parameters for survival. A P value less than 0.05 was considered to be statistically significant.

Results

Patients characterics

Among the 192 patients, 28 (14.6%) were women and 164 (85.4%) were men. The mean age was 57.5 ± 7.8 years, with an age range from 36 to 78 years. The mean CA 242 was 3.36 ± 5.48 U/ml (range: 0.1-49.8 U/ml). The positive rate for CA 242 was 7.3% (14/192) (normal range: 0-10 U/ml).

Analysis of CA 242

A ROC curve for survival prediction was plotted to verify the optimum cuf-off point for CA 242, which was 2.15 (U/ml) (Figure 1). Then, patients were divided into 2 groups for further analysis (patients with CA 242 ≤ 2.15 U/ml and > 2.15 U/ml). The baseline characteristics for patients with CA 242 ≤ 2.15 U/ml and CA 242 > 2.15 U/ml are shown in Table 1. CA 242 were significantly higher in patients with deeply invasive tumors (T3-4a versus T1-2; *P*=0.037), and those associated with node involvement (N1-3 versus N0; *P*=0.029) (Figure 2).

Analysis of survival

The 5-year overall survival was 35.4% by the Kaplan-

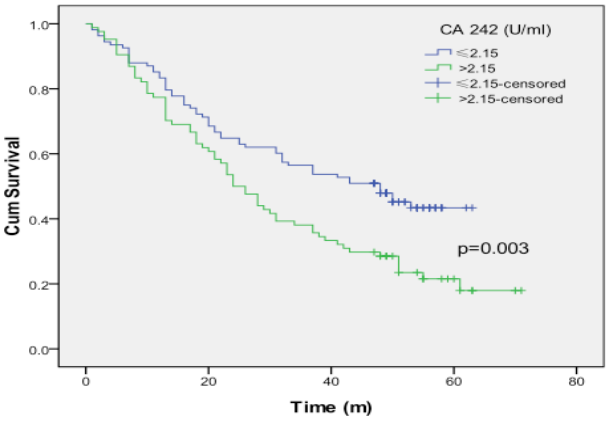

Figure 3. Patients with CA 242 ≤2.15 U/ml Had Significantly Better 5-year Survival Rate than Patients with CA 242 >2.15 U/ml (45.4% versus 22.6%; *P*=0.003)

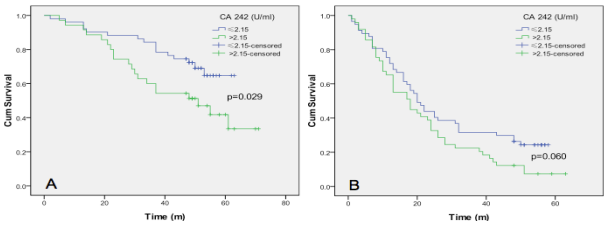

Figure 4. The 5-year Survival of Patients with CA 242 ≤2.15 U/ml was Better than that of Patients with CA 242 >2.15 U/ml When the Nodes were Negative (68.6% versus 42.9%; *P*=0.029) (A). However, there was no significant difference between patients with CA 242 ≤ 2.15 U/ml and >2.15 U/ml when the nodes were positive (24.6% versus 8.2%; *P*=0.060) (B)

Meier method. Patients with CA 242 ≤ 2.15 U/ml had significantly better 5-year survival rate than patients with CA 242 > 2.15 U/ml (45.4% versus 22.6%; *P*=0.003) (Figure 3). The 5-year survival of patients with CA 242 ≤ 2.15 U/ml was better than that of patients with CA 242 > 2.15 U/ml when the nodes were negative (68.6% versus 42.9%; *P*=0.029) (Figure 4A). However, there was no significant difference between patients with CA 242 ≤2.15 U/ml and >2.15 U/ml when the nodes were positive (24.6% versus 8.2%; *P*=0.060) (Figure 4B).

Univariate and multivariate analyses

Univariate analyses were performed to assess the predictive factors. As expected, tumor length, differentiation, CA 242, T grade and N staging were predictive of survival (Table 2). Multivariate analyses demonstrated that differentiation (*P*=0.033), CA 242 (*P*=0.017), T grade (*P*=0.004) and N staging (*P*<0.001) were independent prognostic factors (Table 3).

Discussion

To our knowledge, this may be the first study to determine the prognostic value of CA 242 in ESCC. We used a ROC curve for survival prediction to verify the optimum cuf-off point for CA 242, which was 2.15 U/ml. Our results showed that preoperative CA 242 is a predictive factor for long-term survival in ESCC, especially in nodal-negative patients. We conclude that 2.15 U/ml may be the optimum cuf-off point for CA 242

Table 2. Univariate Analysis of Overall Survival in ESCC Patients

	Survival (%)	HR (95% CI)	*P*-value
Age (years)			0.697
≤60	35.7	1	
>60	34.8	1.076 (0.743-1.559)	
Gender			0.095
Female	50	1	
Male	32.9	1.606 (0.921-2.801)	
Tumor length (cm)			<0.001
≤3	55.8	1	
>3	27.9	2.300 (1.460-3.625)	
Tumor location			0.733
Upper/Middle	35.2	1	
Lower	35.7	1.064 (0.746-1.517)	
Differentiation			0.039
Well/Moderate	37.3	1	
Poorly	25.8	1.615 (1.025-2.543)	
T grade			<0.001
T1-2	62.1	1	
T3-4a	21.4	3.158 (2.030-4.913)	
N staging			<0.001
N0	58.1	1	
N1-3	17	3.534 (2.385-5.238)	
CA 242 (U/ml)			0.003
≤2.15	45.4	1	
>2.15	22.6	1.682 (1.180-2.397)	

Table 3. Multivariate Analysis of Overall Survival in ESCC Patients

	Wald	*P*-value	HR (95% CI)
Age	0.198	0.657	1.090 (0.746-1.591)
Gender	2.127	0.145	1.550 (0.860-2.793)
Tumor length	0.942	0.332	1.278 (0.779-2.097)
Tumor location	0.017	0.895	0.975 (0.668-1.422)
Differentiation	4.571	0.033	1.653 (1.043-2.622)
T grade	8.133	0.004	2.033 (1.248-3.311)
N staging	24.03	<0.001	2.821 (1.864-4.271)
CA 242	5.735	0.017	1.558 (1.084-2.239)

in predicting survival in ESCC.

Accurately understanding the tumor progression status and prognosis of EC before primary treatment will be helpful for oncologists to select adequate therapeutic strategies and improve the quality of life of patients. Lymph node metastases, tumor invasion depth, and in particular, tumor stage, are important prognostic indicators regarded as the gold standard for determining the prognosis of patients with EC (Vallbohmer et al., 2006; Kunisaka et al., 2010). However, it is difficult to accurately determine these prior to surgical treatment. Therfore, with the development of molecular biological techniques and new discoveries in cancer biology, more and more serum tumor markers have been widely explored.

It was proved that CA 242 is involved in tumor invasion and metastasis in case of gastric, pancreatic and colorectal cancer, high CA 242 is associated with poor prognosis (Kuusela et al., 1991; Bünger et al., 2011; Rana et al., 2012). To date, however, there have been few studies regarding CA 242 in EC mainly because of its low sensitivity and specificity, resulting in low detection rates and unacceptable false-positive diagnoses. In our study, the mean CA 242 was 3.36 ± 5.48 U/ml (range: 0.1-49.8

U/ml). When we used a cut-off CA 242 higher than 10 U/ml (normal range: 0-10 U/ml), it was present in only 14 (7.3%) of the 192 patients. Thus, we used a ROC curve for survival prediction to verify the optimum cuf-off point for CA 242, which was 2.15 U/ml. In our study, patients with CA 242 ≤ 2.15 U/ml had significantly better 5-year survival rate than patients with CA 242 >2.15 U/ml (45.4% versus 22.6%; *P*=0.003). CA 242 were significantly higher in patients with deeply invasive tumors (T3-4a versus T1-2; *P*=0.037), and those associated with node involvement (N1-3 versus N0; *P*=0.029).

The potential limitations of the present study include the use of a retrospective analysis and the short duration of the mean follow-up duration. In addition, because the study used data from a single institution but with different pathologists and different surgeons, there may have been a lack of uniformity in measurement methods. Furthermore, we excluded patients who had chemotherapy and/or radiotherapy, which may have influenced our analysis. Thus, larger prospective studies will need to be performed to confirm these preliminary results and determine the optimum cut-off point.

In conclusion, CA 242 is a predictive factor for long-term survival in ESCC, especially in nodal-negative patients. We conclude that 2.15 U/ml may be the optimum cuf-off point for CA 242 in predicting survival in ESCC.

Acknowledgements

The author(s) declare that they have no competing interests.

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