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Prognostic significance of preoperative serum CA 72-4 and CA 242 in patients with esophageal squamous cell carcinoma

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Summary. *Aims:* The aim of this study was to determine the prognostic value of CA 72-4 and CA 242 in esophageal squamous cell carcinoma (ESCC). *Materials and Methods:* From January 2006 to December 2007, a retrospective analysis of 192 consecutive patients with ESCC was carried out. Univariate and multivariate analyses were performed to evaluate the prognostic parameters. *Results:* The positive rates for CA 72-4 and CA 242 were 18.8% (36/192) and 7.3% (14/192), respectively. Patients with CA 72-4 ≤6 U/ml showed a significantly better 5-year overall survival than patients with CA 72-4 >6 U/ml (42.3% vs. 5.6%; p<0.001). Patients with CA 242 ≤10 U/ml also showed a significantly better 5-year overall survival than patients with CA 242 >10 U/ml (37.6% vs. 7.1%; p=0.011). Multivariate analyses demonstrated that differantiation (p=0.021), CA 72-4 (p=0.037), T grade (p=0.012) and N staging (p<0.001) were independent prognostic factors. *Conclusion:* CA 72-4 is an independent predictive factor for long-term survival in ESCC. CA 72-4 shows a higher accuracy in predicting T grades, N stagings and overall survival than CA 242. Although CA 72-4 and CA 242 show significant association with poorer prognosis, its low sensitivity limits the clinical application.

Key words: esophageal squamous cell carcinoma, CA 72-4, CA 242, prognostic factor, survival

«Significatività prognostica del siero preoperativo CA 72-4 e CA 242 in pazienti con carcinoma squamocellulare dell'esofago»

Riassunto. *Scopi:* Lo scopo del presente studio era di determinare il valore prognostico del CA 72-4 e CA 242 in pazienti con carcinoma squamocellulare dell'esofago (ESCC). *Materiali e metodi*: Da gennaio 2006 a Dicembre 2007, è stata effettuata una analisi retrospettiva su 192 pazienti con ESCC. Sono state eseguite analisi univariate e multivariate per valutare i parametri prognostici. *Risultati:* I tassi positivi sono stati rispettivamente del 18,8% (36/192) per il CA 72-4 e 7,3% (14/192) per il CA 242. I pazienti con CA 72-4 ≤6 U/ml hanno mostrato una sopravvivenza complessiva a 5 anni significativamente migliore rispetto ai pazienti con CA 72-4 >6 U/ml (42,3% vs 5.6%; P<0.001). Anche i pazienti con CA 242 ≤10 U/ml hanno dimostrato una sopravvivenza complessiva a 5 anni significativamente migliore rispetto ai pazienti con CA 242 >10 U/ml (37% vs 7,1%; p=0,011). Analisi multivariate hanno dimostrato che la differenziazione (p=0,021), il CA 72-4 (p=0,037), il grado T (p=0,012) e lo stadio N (p<0,001) sono da considerarsi fattori prognostici indipendenti. *Conclusioni*: Il CA 72-4 è un fattore predittivo indipendente per la sopravvivenza a lungo termine nel ESCC. Il CA 72-4 mostra una maggiore accuratezza nei gradi predittivi T, nello stadio N e nella sopravvivenza complessiva rispetto al CA 242. Sebbene CA 72 e CA 242 mostrino una associazione significativa con una prognosi più sfavorevole, la loro bassa sensibilità ne limita l'applicazione clinica.

Parole chiave: carcinoma squamocellulare dell'esofago, CA 72-4, CA 242, fattore prognostico, sopravvivenza

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 (1). 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 (1). Thus, China still suffers a great disease burden from EC. Although advances have occurred in the multidisciplinary treatment, surgical resection is the preferred therapeutic strategy for EC patients. The overall 5-year survival after surgical resection is between 70% and 92% for patients without nodal involvement, but only 18-47% for patients with lymph node metastases (2, 3).

Serum tumour markers play an important role in cancer diagnosis, prognosis, treatment and monitoring. Thus, in order to further improve the survival rate of EC patients, it is essential to explore and identify relevant biomarkers with adverse prognosis. The aim of this study was to determine the prognostic value of preoperative CA 72-4 and CA 242 in esophageal squamous cell carcinoma (ESCC).

Materials and Methods

Patients

A retrospective analysis was carried out 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 6 lymph nodes were examined for pathological diagnosis; 4) esophagectomy was neither preceded nor followed by adjuvant chemotherapy and/or radiotherapy; and 5) serum CA 72-4 and CA 242 were obtained before esophagectomy. In addition, we excluded patients with non-ESCC, gastroesophageal junction carcinoma, and patients who underwent surgical exploration but without curative esophagectomy.

All of the above patients were followed up by posting letters or by telephone interviews. The last follow-up was 30 November 2011. All subjects gave their written informed consent to the study protocol, which was approved by the Ethical Committees of Zhejiang Cancer Hospital, Hangzhou, China.

Surgery

The left transthoracic procedure and Ivor-Lewis procedure with anastomosis of the upper chest were performed for all tumours of the lower thoracic esophagus and some tumours of the middle thoracic esophagus. The McKeown procedure was used for all tumours of the upper thoracic esophagus and some tumours of the middle thoracic esophagus. In our institute, the majority of patients underwent two-field lymphadenectomy. Three-field lymphadenectomy was performed only if the cervical lymph nodes were thought to be abnormal. 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 (4).

CA 72-4 and CA 242 analysis

The peripheral blood was obtained at the preoperative workup. Serum CA 72-4 and CA 242 were detected through immunoradiometric assay. The cut-off values for serum CA 72-4 and CA 242 were 6 U/ml and 10 U/ml, respectively.

Statistical analysis

Statistical evaluation was carried out with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). 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. In order to further evaluate and compare the predictive tumour markers, we used receiver operating characteristic (ROC) curves for censored data and the area under the ROC curve (AUC) as the criterion. A p value less than 0.05 was considered to be statistically significant.

Results

Patients characteristics

The baseline characteristics are shown in Table 1 and Table 2. The positive rates for CA 72-4 and CA 242 were 18.8% (36/192) and 7.3% (14/192), respectively. Serum CA 72-4 and CA 242 were significantly higher in patients with nodal involvement (Figure 1).

Overall survival

The 5-year overall survival was 35.4% by the Kaplan-Meier method. Patients with CA 72-4 ≤6 U/ml showed a significantly better 5-year overall survival than patients with CA 72-4 >6 U/ml (42.3% vs. 5.6%; p<0.001) (Figure 2A). Patients with CA 242 ≤10 U/ml also showed a significantly better 5-year overall survival than patients with CA 242 >10 U/ml (37.6% vs. 7.1%; p=0.011) (Figure 2B).

Prognostic analysis

Univariate analyses were performed to assess the predictive factors. As expected, tumour length, differ-

Table 1. The baseline characteristics of 192 patients with ESCC

	Cases (n, %)
Age (mean ± SD, years)	57.5±7.8
Gender	
Female	28 (14.6)
Male	164 (85.4)
Tumour length (mean ± SD, cm)	4.35±1.76
CA 72-4 (mean ± SD, U/ml)	4.64±5.42
CA 242 (mean ± SD, U/ml)	3.36±5.48
Tumour location	
Upper	11 (5.7)
Middle	97 (50.5)
Lower	84 (43.8)
Histologic type	
Well	23 (12.0)
Moderate	138 (71.9)
Poor	31 (16.1)
T grade	
T1	29 (15.1)
T2	37 (19.3)
T3	108 (56.2)
T4a	18 (9.4)
N staging	
N0	86 (44.8)
N1	52 (27.1)
N2	42 (21.9)
N3	12 (6.2)

Table 2. Comparison of clinicopathological variables in CA 72-4 and CA 242

	CA 72-4 (U/ml)		P-value	CA 242 (U/ml)		P-value
	≤6 (n, %)	>6 (n, %)		≤10 (n, %)	>10 (n, %)	
Age (years)			0.307			0.913
≤60	105 (67.3)	21 (58.3)		117 (65.7)	9 (64.3)	
>60	51 (32.7)	15 (41.7)		61 (34.3)	5 (35.7)	
Gender			0.513			0.413
Female	24 (15.4)	4 (11.1)		27 (14.1)	1 (7.1)	
Male	132 (84.6)	32(88.9)		151 (85.9)	13 (92.9)	
Tumour length (cm)			0.775			0.450
≤3.0	43 (27.6)	9 (25.0)		47 (26.4)	5 (35.7)	
>3.0	113 (72.4)	27 (75.0)		131 (73.6)	9 (64.3)	
Tumour location			0.780			0.624
Upper/Middle	87 (55.8)	21 (58.3)		101 (56.7)	7 (50.0)	
Lower	69 (44.2)	15 (41.7)		77 (43.3)	7 (50.0)	
Histologic type			0.362			0.342
Well/Moderate	129 (82.7)	32 (88.9)		148 (83.1)	13 (92.9)	
Poor	27 (17.3)	4 (11.1)		30 (16.9)	1 (7.1)	
T grade			0.013			0.289
T1-2	60 (38.5)	6 (16.7)		63 (35.4)	3 (21.4)	
T3-4a	96 (61.5)	30 (83.3)		115 (64.6)	11 (78.6)	
N staging			0.003			0.017
N0	78 (50.0)	8 (22.2)		84 (47.2)	2 (14.3)	
N1-3	78 (50.0)	28 (77.8)		94 (52.8)	12 (85.7)	

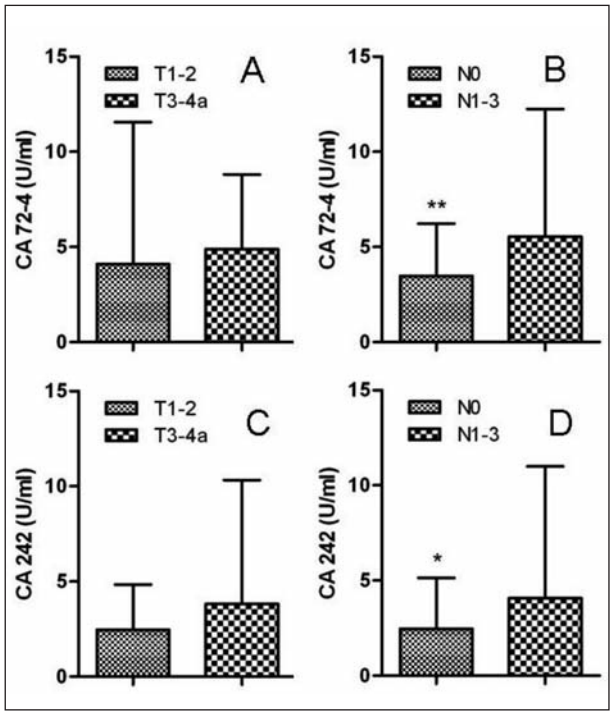

Figure 1. Serum CA 72-4 in T grades (A) and N stagings (B). Serum CA 242 in T grades (C) and N stagings (D). (*<0.05; **<0.01)

entiation, CA 72-4, CA 242, T grade and N staging were predictive of survival (Table 3). Then multivariate analyses were performed with the Cox proportional hazards model. In that model, we demonstrated that differantiation (p=0.021), CA 72-4 (p=0.037), T grade (p=0.012) and N staging (p<0.001) were independent prognostic factors (Table 4).

ROC curve analysis

The ROC curves analyses of preoperative serum CA 72-4 and CA 242 for T grades (T1-2 vs. T3-4a), N stagings (N0 vs. N1-3) and overall survival (survival vs. death) are shown in Figure 3.

Discussion

To our knowledge, this may be the first study to determine the prognostic value of CA 72-4 and CA 242 in ESCC. Our results clearly showed that patients with higher CA 72-4 or CA 242 had a worse 5-year overall survival compared to those within normal range. We also demonstrated that CA 72-4 is a predictive factor for long-term survival in ESCC.

Accurately understanding the tumour progression status and prognosis of EC before primary treatment will be helpful for oncologists to select adequate

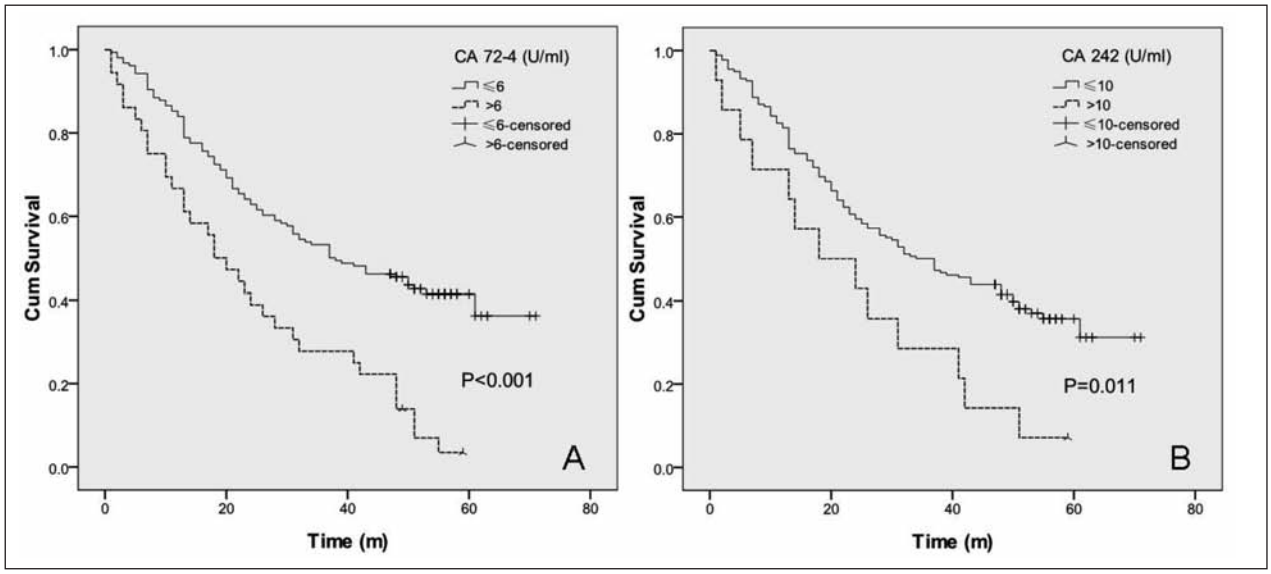

Figure 2. Patients with CA 72-4 ≤6 U/ml showed a significantly better 5-year overall survival than patients with CA 72-4 >6 U/ml (42.3% vs. 5.6%; p<0.001) (A). Patients with CA 242 ≤10 U/ml also showed a significantly better 5-year overall survival than patients with CA 242 >10 U/ml (37.6% vs. 7.1%; p=0.011) (B).

Table 3. Univariate analysis of overall survival in ESCC patients

	5-year survival (%)	HR (95% CI)	P-value
Age (years)			0.697
≤60	35.7	1.000	
>60	34.8	1.076 (0.743-1.559)	
Gender			0.095
Female	50.0	1.000	
Male	32.9	1.606 (0.921-2.801)	
Tumour size (cm)			0.000
≤3	55.8	1.000	
>3	27.9	2.300 (1.460-3.625)	
Tumour location			0.733
Upper/Middle	35.2	1.000	
Lower	35.7	1.064 (0.746-1.517)	
Differentiation			0.039
Well/Moderate	37.3	1.000	
Poorly	25.8	1.615 (1.025-2.543)	
T grade			0.000
T1-2	62.1	1.000	
T3-4a	21.4	3.158 (2.030-4.913)	
N staging			0.000
N0	58.1	1.000	
N1-3	17.0	3.534 (2.385-5.238)	
CA 72-4 (U/ml)			
≤6	42.3	1.000	0.000
>6	5.6	2.390 (1.606-3.557)	
CA 242 (U/ml)			0.011
≤10	37.6	1.000	
>10	7.1	2.053 (1.154-3.652)	

ESCC: esophageal squamous cell carcinoma; HR: hazard ratio; CI: confidence interval

Table 4. Multivariate analysis of overall survival in ESCC patients

	HR (95% CI)	P-value
Age	1.036 (0.707-1.516)	0.858
Gender	1.562 (0.861-2.834)	0.142
Tumour length	1.332 (0.805-2.206)	0.265
Tumour location	0.942 (0.646-1.374)	0.756
Differentiation	1.737 (1.088-2.773)	0.021
T grade	1.883 (1.148-3.091)	0.012
N staging	2.710 (1.773-4.143)	0.000
CA 72-4	1.609 (1.029-2.514)	0.037
CA 242	1.014 (0.524-1.961)	0.967

ESCC: esophageal squamous cell carcinoma; HR: hazard ratio; CI: confidence interval

therapeutic strategies and improve the patients' quality of life. Lymph node metastases, tumour invasion depth, and in particular, tumour stage, are important prognostic indicators currently regarded as the gold standard for determining the prognosis of patients with EC (5, 6). However, it is difficult to accurately determine them prior to surgical treatment. With the development of molecular biological techniques and new discoveries in cancer biology, more and more serum tumour markers have been widely explored.

To date, few studies regarding CA 72-4 and CA 242 in EC mainly because of its low sensitivity and specificity have been carried out. Lopez et al. (7) showed that the sensitivity of CA 72-4 was 18% in EC. Brockmann *et al.* (8) showed that CA 72-4 revealed a low sensitivity of 16%. However, higher concentrations were found in adenocarcinoma (8). In our study, the positive rates for CA 72-4 and CA 242 were 18.8% and 7.3%, respectively. We demonstrated that serum CA 72-4 and CA 242 were significantly higher in patients with nodal involvement. Although the sensitivity and specificity were low in our study, patients with higher CA 72-4 or CA 242 had a worse 5-year survival compared to those with normal range.

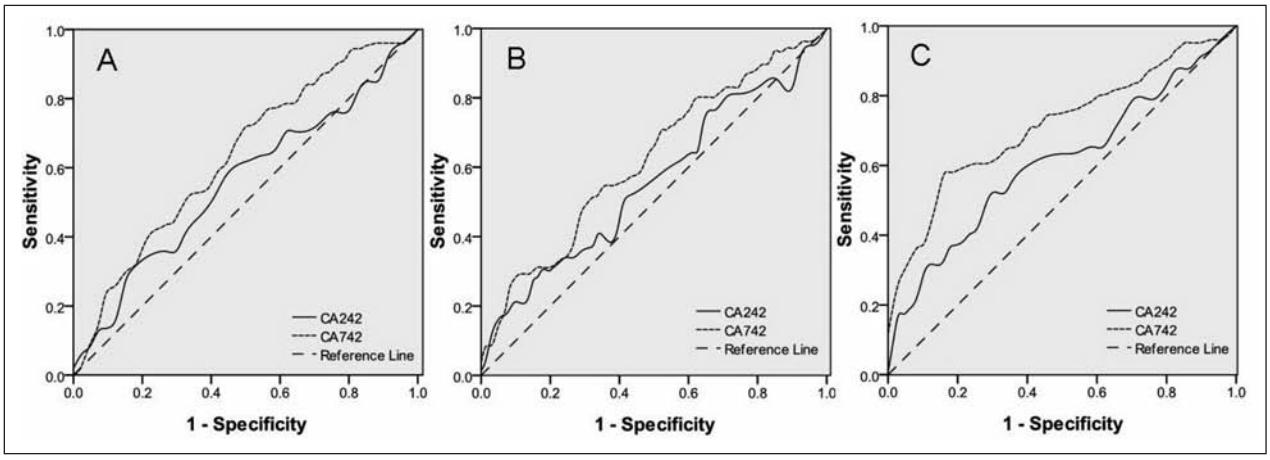

Figure 3. CA 72-4 showed a higher accuracy in predicting T grades (CA 72-4: AUC 0.633 vs. CA 242: AUC 0.558; Fig. A), N stagings (CA 72-4: AUC 0.620 vs. CA 242: AUC 0.557; Fig. B) and overall survival (CA 72-4: AUC 0.715 vs. CA 242: AUC 0.607; Fig. C) than CA 242 by ROC curves.

In addition, we used ROC curves for censored data and the AUC as the criterion. In our study, we demonstrated that CA 72-4 showed a higher accuracy in predicting tumour invasion depth, lymph node metastases and overall survival than CA 242.

It has been reported that tumour markers are elevated in patients with recurrence. Kim *et al.* (9) indicated that postoperative findings of increased serum CA 72-4 in patients who underwent curative radical gastrectomy are more important indicators of recurrence than preoperative findings of positivity. Marrelli *et al.* (10) demonstrated that the sensitivity for recurrence of postoperative CA 72-4 was 51%. They also indicated that perioperative CA 72-4 is a good follow-up test with a higher degree of specificity after surgery. However, no studies regarding CA 72-4 and CA 242 in EC recurrence have been carried out. Thus, larger prospective studies will need to be performed in order to confirm these preliminary results in EC.

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, a lack of uniformity in measurement methods may have been present. Furthermore, due to the limited number of patients with positive rate of CA 72-4 or CA 242, our analysis may suffer from type I or type II error. The results of the study should therefore be regarded with caution. Thus, further studies are needed to explore its long-term effect.

In conclusion, CA 72-4 is an independent predictive factor for long-term survival in ESCC. CA 72-4 shows a higher accuracy in predicting T grades, N stagings and overall survival than CA 242. Although CA 72-4 and CA 242 show significant association with poorer prognosis, its low sensitivity limits the clinical application.

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