RESEARCH ARTICLE

Tumor Markers for Diagnosis, Monitoring of Recurrence and Prognosis in Patients with Upper Gastrointestinal Tract Cancer

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Abstract

To evaluate the value of combined detection of serum CEA, CA19-9, CA24-2, AFP, CA72-4, SCC, TPA and TPS for the clinical diagnosis of upper gastrointestinal tract (GIT) cancer and to analyze the efficacy of these tumor markers (TMs) in evaluating curative effects and prognosis. A total of 573 patients with upper GIT cancer between January 2004 and December 2007 were enrolled in this study. Serum levels of CEA, CA19-9, CA24-2, AFP, CA72-4, SCC, TPA and TPS were examined preoperatively and every 3 months postoperatively by ELISA. The sensitivity of CEA, CA19-9, CA24-2, AFP, CA72-4, SCC, TPA and TPS were 26.8%, 36.2%, 42.9%, 2.84%, 25.4%, 34.6%, 34.2% and 30.9%, respectively. The combined detection of CEA+CA199+CA242+CA724 had higher sensitivity and specificity in gastric cancer (GC) and cardiac cancer, while CEA+CA199+CA242+SCC was the best combination of diagnosis for esophageal cancer (EC). Elevation of preoperative CEA, CA19-9 and CA24-2, SCC and CA72-4 was significantly associated with pathological types ($p<0.05$) and TNM staging ($p<0.05$). Correlation analysis showed that CA24-2 was significantly correlated with CA19-9 ($r=0.810$, $p<0.001$). The levels of CEA, CA19-9, CA24-2, CA72-4 and SCC decreased obviously 3 months after operations. When metastasis and recurrence occurred, the levels of TMs significantly increased. On multivariate analysis, high preoperative CA72-4, CA24-2 and SCC served as prognostic factors for cardiac carcinoma, GC and EC, respectively. combined detection of CEA+CA199+CA242+SCC proved to be the most economic and practical strategy in diagnosis of EC; CEA+CA199+CA242+CA724 proved to be a better evaluation indicator for cardiac cancer and GC. CEA and CA19-9, CA24-2, CA72-4 and SCC, examined postoperatively during follow-up, were useful to find early tumor recurrence and metastasis, and evaluate prognosis. AFP, TPA and TPS have no significant value in diagnosis of patients with upper GIT cancer.

Keywords: Upper gastrointestinal tract cancer - tumor markers - diagnosis - monitoring - prognosis

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Introduction

EC, Cardia cancer and GC are three of the most commonly seen malignant tumors of GIT cancer.

EC is one of the most aggressive neoplasms. One characteristic of EC is its incidence diversity, with high indices in Asian countries and a milder incidence in European and American continents (Zheng et al., 2010; Lin et al., 2013). China is one of the high incidence areas of EC, particular in Henan, Hebei, and Shanxi in Central North China, which have the highest incidence rates in the world.

GC is a desease with high morbidity and mortality. Two-thirds of the GC cases occur in developing country. Among them, more than 40% of cases are located in china. Although GC has shown a significant decline in morbidity in recent years, but it still ranks second among all malignant tumors in china and is younger. In contrast with GC, cardia cancer has shown a relatively increased in incidence. Due to the anatomical characteristics of cardiac, cardia cancer are diagnosed already at advanced stages of the disease. Most of treatment outcomes of patients have been poor because the disease has already progressed to an advanced stage by the time it is diagnosed. Consequently, various tumor markers have been used to detect cancer at an early stage and monitor cancers.

Recent researches and clinical practices indicate that there are some tumor markers (TMs), including the carcinoembryonic antigen (CEA), saliva acidification fucus pentose antigen (CA19-9), gastrointestinal carcinoma (CA24-2), a tire protein (AFP) and gastric cancer and ovarian cancer antigen (CA72-4), squamous cell carcinoma antigen (SCC), tissue polypeptide antigen (TPA), cytokeratin 18 (TPS) are commonly found in

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digestive tract, lung and ovary carcinomas (Schneider et al., 2003; Molina et al., 2005; Buyru et al., 2006; Grinbaum et al., 2006; Fernandes et al., 2007; Wu et al., 2007; Chen et al., 2008). Moreover, they can be used for the monitoring of tumor recurrence and used as prognostic factors.

However, the sensitivity of one TM is low, but the combination of these TMs has not been used to evaluating curative effect and prognosis of upper GIT cancers, especially all the EC, GC and cardia cancer. We conducted the present study to explore the relationship between the clinical characteristics of patients with upper GIT cancer and TMs, and to evaluate the predictive and prognostic value of preoperative serum levels of TMs for upper GIT cancer.

Materials and Methods

Patients and blood samples

The study included 573 patients who underwent surgical resection for primary upper GIT cancer between January 1, 2004 and December 30, 2007. Of the 573 patients, 463 underwent radical surgery and 110 underwent palliative surgery, with a median age of 58.4 years (range 29 ~ 81 years). Among them, 127 cases were EC, 264 were GC and 182 were cardia carcinoma. In 573 patients, 129 underwent comprehensive treatment after operation, which included stage I (n=3), II (n=20), III (n=82) and IV (n=24), according to the International Tumor Node Metastasis (TNM) staging system. The TNM staging for EC was performed according to NCCN (2002); cardia cancer and GC according to the AJCC (2003). All cases were confirmed by pathological histology and cytology examination. No chemotherapy and radiotherapy was accepted preoperation. No main organ dysfunction was found in these patients and normal bone marrow, liver and renal functions were assessed for inclusion in the study. Patients characteristics are presented in Table 1.

Table 1. Patients and Disease Characterisitics (n=573)

Characteristics	N
Gender	
Males/Females	440/133
Age (years)	
≤40/>40	138/435
Localisation of primary tumor	
Esophagealcancer/Cardiac carcinoma /Gastric cancer	127/182/264
Histological type	
Squamous cell carcinomas/Adenocarcinoma	135/427
TNM	
I/II/III/IV	41/138/302/81
Status at last follow-up	
Alive/Dead	222/138

Follow-up

Overall, 360 patients were followed-up at the outpatient clinic after hospital discharge. 213 cases were lost to follow-up. The follow-up system consisted of measurement of serum TMs routinely at 3-month intervals for the first year, and at 6-month intervals thereafter. The follow-up program included: clinical examination, hematological analyses and TM assay at each checkup; abdominal ultrasound and chest x-rays were scheduled every 6 months. Criteria for the establishment of recurrent disease included histological confirmation, palpable disease, or disease evident radiologically with subsequent clinical progression and supportive biochemical data. The follow-up end-date was Mar 1, 2010. All survival patients were followed-up for at least 36 months. 138 patients died during the follow-up period.

Tumor marker assay

Peripheral blood from patients was obtained at the preoperative workup and three months after comprehensive treatment. And the samples were collected and then centrifuged for 10 minutes at 3000 rpm; serum was then immediately separated for examination. Serum CEA, CA19-9, CA24-2, AFP, SCC, CA72-4, TPA and TPS were measured by ELISA using TECAN and reagent kits (Sweden and IDL Biotech), with CEA>3μg/L, CA19-9>20 U/ml, CA24-2>12 U/ml, AFP>15μg/L, SCC>1 ng/ml, CA72-4 >5 ng/ml, TPA>2 ng/ml and TPS>150 U/L being regarded as elevated status. The cut-off values of these TMs were previously established by our laboratory by taking into account several factors (as diet, living conditions and patient selection).

Statistical analyses

Statistical analysis was carried out using SPSS 16.0 software. The TMs levels of two groups were compared using Wilcoxon test; differences in several serum markers' levels were evaluated by Kruskal-Wallis test. Correlation

Table 2. Sensitivity and Specificity of Combination of TMs in Detecting EC, Cardiac Cancer and GC

	EC		Cardiac cancer and GC	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
CEA+CA199	18.4	67.5	59.3	89.6
CEA+CA199+CA724	23.5	63.4	68.7	88.0
CEA+CA199+CA242	28.9	60.2	71.5[d]	88.9
CEA+CA199+CA242+CA724	31.8	59.8	82.6[e]	83.3
CA199+CA242+CA724	22.6	61.2	63.0	83.4
CEA+SCC	52.3[a]	72.8	34.6	87.9
CEA+CA199+CA242+SCC	68.4[b]	71.5	73.1	87.2
CEA+CA199+CA724+SCC	65.7	70.8	64.5	80.5
CEA+CA199+CA242+CA724+SCC	70.8	69.9	83.6	80.7
CEA+CA199+CA242+CA724+SCC+TPA	71.5	60.5	84.5	76.5
CEA+CA199+CA242+CA724+SCC+TPA+TPS	73.2[c]	56.4	84.9[f]	74.5

*bCompared with a, p<0.05; b Compared with c, p>0.05; e Compared with d, p<0.05; e Compared with f, *p*>0.05

Table 3. Relationship between Positive Rate of TMs and the Pathological Types, TNM Staging in Upper Gastrointestinal Cancer Patients (%)

Item	CEA	CA19-9	CA24-2	AFP	SCC	CA72-4	TPA	TPS
pathological types								
Squamous cell carcinomas								
	14.1 (19/135)	13.8 (18/135)	20.7 (27/135)	0 (0/135)	30.3 (41/135)	5.8 (8/135)	27.3 (37/135)	24.1 (37/135)
Adenocarcinoma	32* (139/427)	52.6* (225/427)	56.4* (241/427)	6.3*) (27/427	9.8* (42/427)	50.68* (216/427)	37.2 (159/427)	33.5 (143/427)
X^2	8.948	9.992	11.479	5.376	4.553	13.834	2.176	1
p	0.003	0.002	0.001	0.02	0.033	0.001	0.14	0.317
TNM staging								
I+II	20.6 (36/179)	14 (25/179)	19.6 (35/179)	3.9 (7/179)	20.6 (37/179)	6.8 (12/179)	12.8 (23/179)	30.7 (55/179)
III	29.4** (89/302)	33.1** (100/302)	38.4** (116/302)	1.6 (5/302)	15.4** (47/302)	29.84** (90/302)	29.4** (89/302)	28.4 (86/302)
IV	35.8*** (29/81)	53.4*** (43/81)	59.2*** (48/81)	7.4 (6/81)	37.0*** (30/81)	54.38*** (44/81)	42.0*** (34/81)	41.9 (34/81)
X^2	5.13	19.412	21.3	6.76	12.321	6.901	14.35	1
p	0.034	0	0	0.077	0.002	0.032	0	0.317

*compared with squamous cell carcinomas; **compared with I+II and IV; ***compared with I+II and III

Table 4. Correlation between Serum Levels of TMs in Upper Gastrointestinal Cancer Patients and Sex and Age (M+Q)

Item	CEA (ug/l)	CA19-9 (U/ml)	CA24-2 (U/ml)	AFP (ug/l)	SCC (ng/ml)	CA72-4 (U/ml)	TPA (ng/ml)	TPS (U/l)
Sex								
Male	10.41+	50.86+	35.45+	6.54+	2.57+	18.71+	1.59+	101.18+
(n=440)	3.67	14.86	14.14	2.87	0.56	2.16	1.54	108.6
Female	6.65+	75.18+	56.43+	5.69+	2.18+	10.57+	1.57+	88.90+
(n=133)	1.63	31.76	28.48	2.45	0.62	1.47	1.75	75.54
p	0	0.002	0.003	0.43	0.284	0.029	0.605	0.231
Age(yr)								
≤40	8.94+	63.26+	40.36+	1.70+	2.65+	14.64+	1.65+	101.18+
(n=138)	2.3	22.71	19.57	2.48	0.56	1.93	1.79	97.94
>40	12.82+	69.54+	46.58+	2.01+	2.09+	15.61+	1.51+	88.910+
(n=435)	3.37	13.82	13.18	3.41	0.59	2.2	1.32	102.79
p	0.035	0.644	0.109	0.22	0.561	0.628	0.239	0.398

*M (Median); Q (Interquartile range)

between CEA, CA19-9, CA24-2, CA72-4, TPS, TPA and SCC was used Spearman analysis.The two groups were compared by cross-table analysis using Pearson's chi-square test. Overall survival rates were calculated by the Kaplan-Meier method, and the differences in survival rates were analyzed by the log-rank test. P-value of less than 0.05 was considered to be statistically significant.

Results

In the 573 cases, the sensitivity of CEA, CA19-9, CA24-2, AFP, SCC, CA72-4, TPA and TPS were 26.80%, 36.15%, 42.89%, 2.84%, 25.39%, 34.59%, 34.15% and 30.89% in upper GIT cancer, respectively. The combined detection of CEA+CA199+CA242+CA724 had higher sensitivity and specificity in GC and Cardiac cancer, while CEA+CA199+CA242+SCC was the best combination of diagnosis for EC (Table 2). Tumor marker serum levels were related to histological type, with SCC being the most sensitive marker in squamous cell carcinomas, especially EC, CEA, CA19-9, CA24-2 and CA72-4 in adenocarcinoma. However, serum TPA and TPS levels did not correlate with pathological types, and AFP and TPS did not correlate with TNM staging (Table 3).

The CEA and CA72-4 levels in male (10.41+3.67ug/ml, 18.71+2.16 U/ml) were significantly higher than their respective levels in female (6.65+1.63ug/ml, 10.57+1.47 U/ml). Conversely, CA19-9 and CA24-2 levels in female (75.18+31.76 U/ml, 56.43+28.48 U/ml) were significantly higher than in male (50.86,+14.86 U/ml, 35.45+14.14 U/ml). Elevated serum levels of CEA were detected preoperatively in high age group ($p<0.05$) (Table 4).

Correlation analysis showed that preoperative level of CA24-2 siginificantly correlated with CA19-9 ($r=0.810$, $p<0.01$).

Compared with preoperative concentrations, the levels of CEA, CA19-9, CA24-2, CA72-4 and SCC significantly decreased 3 months after operation ($p<0.005$). When metastasis and recurrence occurred, the levels of these markers significantly increased (Table 5).

The follow-up time for this study was from 6 months to 38months. All survival patients were followed-up for at least 36 months. Overall 138 patients died during the follow-up period. The levels of TMs generally increased during follow-up while metastasis and/or deterioration increasingly occurred. The longest time interval between the increasing levels of the TMs and the appearance of

Table 5. Serum Levels of TMs Pre-and Post-operation (M+Q)

Item	CEA (ug/l)	CA19-9 (U/ml)	CA24-2 (U/ml)	AFP (ug/l)	SCC (ng/ml)	CA72-4 (U/ml)	TPA (ng/ml)	TPS (U/l)
Pre-	9.58+	68.25+	42.28+	2.50+	2.16+	13.64+	1.19+	77.45+
operation	1.90*	13.21*	9.96*	3.58	0.67*	3.54*	1.52	104.11
3months	1.01+	23.54+	16.58+	2.40+	0.41+	7.89+	1.14+	74.18+
post-operation	1.37	8.25	8.21	3.3	0.74	1.15	1.5	80.28
Recurrence	12.58+	78.36+	46.98+	3.58+	2.05+	16.53+	1.36+	89.64+
and Metastasis	2.34**	10.25**	8.97**	2.31	0.64**	3.67**	0.97	79.6
P	<0.005	<0.005	<0.005	>0.05	<0.005	<0.005	>0.05	>0.05

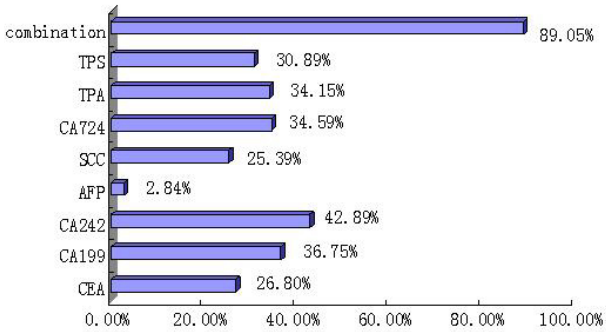

Figure 1. Sensitivity of TMs in Upper Gastrointestinal Cancer

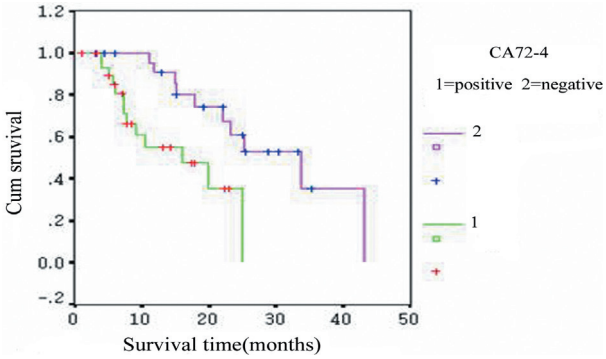

Figure 2. Overall Survival Curves For Cardiac Carcinoma Patients with CA72-4≤5 and CA72-4>5ng/ml

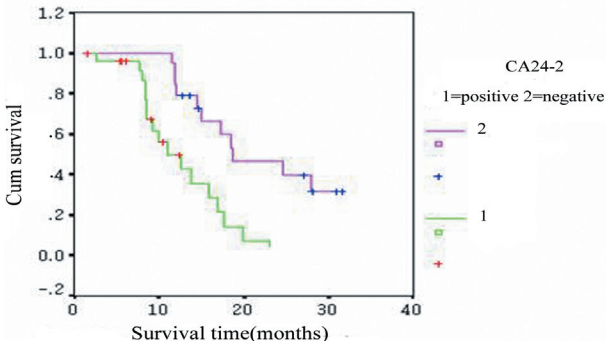

Figure 3. Overall Survival Curves for Gastric Cancer Patients with CA24-4≤12 and CA24-4>12U/ml

the imaging features was 124 days. Elevated marker levels indicated poorer survival. Multivariate analysis indicated that preoperatively CA72-4, CA24-2 and SCC were prognostic factors of cardiac carcinoma, GC and EC, respectively. Median survival time for cardiac carcinoma with negative preoperative CA72-4 was 33.6 months, and was 16.3 months for patients with preoperative CA72-4 positive levels (p<0.005). Similarly, the median survival time for GC with negative preoperative CA24-2

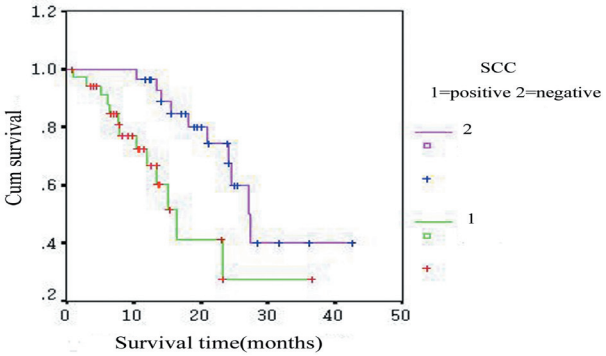

Figure 4. Overall Survival Curves for Esophageal Cancer Patients with SCC≤1 and SCC>1ng/ml

was 18.1 months, and was 10.9 months for patients with preoperative CA24-2 positive levels (p<0.001), while the median survival time for esophagus cancer was 27.4 months and 16.5 months in patients with SCC negative levels and positive levels (p<0.005) (Figure 2-4).

Discussion

EC, cardia cancer and GC are common malignant upper GIT cancer in the world. In China, the incidence and mortality rates are more than twice of the world average. Shanxi is a high incidence area of upper GIT cancer. Among these, 90% of EC are esophageal squamous carcinoma, whereas most of cardiac cancer and GC are adenocarcinoma. As the cancers occured mostly in remote areas, most patients are diagnosed already at an advanced stage.

Surgery is the main approach for upper GIT cancer, and the most important prognostic factor of upper GIT cancer is tumor node metastasis (TNM) classification (Edge et al., 2010). However, it is difficult to obtain complete data preoperatively. For this reason, it may be important to find some other preoperative prognostic factors for evaluating the outcome of upper GIT cancer patients. TMs have been used for the early screening, diagnosis, evaluating prognosis, monitoring curative effect, and detecting relapse in patients of cancer (Bates et al., 1991; Nishimaki et al., 1999; Nishimaki et al., 1999; Zhang et al., 2009). However, each TM has its limitation in terms of diagnostic value, especially for the early diagnosis (Marrelli et al., 2004; Patriti et al., 2007). It is therefore necessary to find new molecules and combination of several of these TMs at the same time (Wang et al., 2005; Gao et al., 2007; Gupta et al., 2007; Park et al., 2007; Gao et al., 2007).

In the study, we detected serum levels of CEA, CA19-9, CA24-2, AFP, CA72-4, SCC, TPA and TPS

in 127 patients with EC, 182 with Cardiac cancer and 264 with GC. Different studies have reported different rates of these tumor markers. Whatever Combination of multiple markers can improve overall detection sensitivity. Tian et al. indicated CEA, CA19-9, CA24-2 and CA50 maybe better combinations in improving diagnostic accuracy of GC (Tian et al., 2014). In the present study, we found the most sensitive combinations of tumor markers were CEA+CA199+CA242+SCC in EC; while CEA+CA199+CA242+CA724 proved to be a better evaluation indicator to cardiac cancer and GC. Therefore, these tumor markers can be used for auxiliary diagnosis of patients with upper GIT cancer and preliminary judgment for pathological types.

The positive rates of CEA, CA19-9, CA24-2, and CA72-4 were strongly related to TNM staging, consistent with other studies (Safi et al., 1995; Marrelli et al., 1999; Ychou et al., 2000; Carpelan et al., 2002; Mandorwski et al., 2002; Mandorwski et al., 2002; Jing et al., 2013), and the levels of these TMs increased according to the progression of the tumor. Other study reported that no correlation exists between CEA, CA19-9 and tumor stage (Hee et al., 2014). Tian et al. found elevated levels of CEA, CA19-9 and CA24-2 were associated with advanced tumor stage (Tian et al., 2014). Abdullah et al. showed no significant correlation between CEA, CA19-9 and advanced stages, however, the high levels of CA19-9 suggested a more advanced tumor stage (Abdullah et al., 2013). Also, the positive rate of SCC significantly correlated with TNM staging (Nakamura et al., 1998; Kosugi et al., 2004; Takemura et al., 2004).

We detected a significant association between CEA, CA19-9, CA24-2, SCC and CA72-4 and pathological types. The SCC was the most sensitive marker in squamous cell carcinomas, especially EC, CEA, CA19-9, CA24-2 and CA72-4 in adenocarcinoma. Similar to the findings, CEA, CA19-9, CA24-2 and CA72-4 had high positive rates in cardiac carcinoma and GC (Oremek et al., 2003), and SCC had high positive rate in EC (Shimada et al., 2003). Did not found relationship between either CEA or CA19-9 positivity and histopathology type, but they analyzed the levels of CA24-2 in GC, finding that serum CA24-2 has superior value in GC (Tian et al., 2014). The preoperative serum CEA and CA19-9 has been reported as a prognostic factor in GC (Choi et al., 2006; Xiao et al., 2014). Showed that preoperative CA24-2 was a predictive factor for long-term survival (Feng et al., 2013). In our study, survival analysis revealed that elevated preoperative levels of serum CA72-4, CA24-2 and SCC indicated the poor survival of Cardiac cancer, GC and EC, respectively. Therefore, preoperative serum CA72-4 (Goral et al., 2007; Ucar et al., 2008), CA24-2 and SCC levels may be useful predictors (Mao et al., 2003 ; Kosugi et al., 2004).

Our results showed that CEA and CA72-4 levels were significantly higher in male patients than in female, whereas CA19-9 and CA24-2 levels in female were significantly higher than in male, which was similar to our previous finding. It needs to be further discussed.

Spearman analysis showed that preoperative level of CA19-9 significantly correlated with CA24-2 ($r=0.810$, $p<0.001$), as there may be similarities in the mechanism of generation of the two markers, suggesting that a combination test of CA19-9 and CA24-2 can improve the possibilities for the screening or monitoring disease recurrence and response to treatment.

Compared with preoperative levels, postoperative TMs levels significantly decreased. When metastasis and recurrence occurred, the CEA, CA19-9, CA24-2, SCC, and CA72-4 levels increased again in compared with postoperative concentrations. Our findings are similar to those of Takahashi et al. (2003) who reported that in most patients with high preoperative TMs levels, these TMs increased again at recurrence or metastasis. The finding indicated that patients, who with high preoperative tumor markers levels, and/or at stage II/III/IV need comprehensive treatment. The levels of TMs generally increased during follow-up while metastasis and deterioration increasingly occurred and were related to the burden of the tumor. The elevated levels of TMs appeared earlier than the sensitive imaging results when the tumor recurred, with the longest interval being of 124 days. Therefore, these TMs could play an important role in the monitoring of tumor recurrence and metastasis, thus allowing identifying symptomless patient with tumor recurrence by routine postoperative serum TMs checkups.

In conclusion, combined detection of CEA+CA199+CA242+SCC proved to be the most economic and practical strategy in diagnosis of EC; CEA+CA199+CA242+CA724 proved to be a better evaluation indicator to cardiac cancer and GC. The CEA and CA19-9, CA24-2, CA72-4 and SCC, examined postoperatively during follow-up, were useful to find early tumor recurrence and metastasis, and evaluate prognosis. AFP, TPA and TPS have no significant value in diagnosis patients with upper GIT cancer.

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