RESEARCH ARTICLE

Preliminary Evaluation of Clinical Utility of CYFRA 21-1, CA 72-4, NSE, CA19-9 and CEA in Stomach Cancer

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Abstract

Background: Although various tumor markers have been utilized in management of stomach cancer (SC), only a few reports have described relevance of examples such as CYFRA 21-1 and neuron-specific enolase (NSE). The purpose of this study was to evaluate the potential diagnostic performance of carcinoembryonic antigen (CEA), CA 19-9, CA72-4, CYFRA 21-1 and NSE in patients with SC. Materials and Methods: Ninety-six SC patients with pathologic confirmation between 2012 and 2013 were enrolled. Serum levels of five tumor markers were analyzed using a solid-phase immunoradiometric assay. Receiver operating characteristic (ROC) curves were plotted for the five tumor markers to investigate their diagnostic powers and adjusted cutoff values derived from analysis of ROC curves were evaluated to calculate the sensitivity of each for SC with recommended cutoff values. Results: Based on two different cutoff values (recommended and adjusted), CYFRA 21-1 (≥2.0 and 1.2 ng/ml) had a respective sensitivity of 50% and 78.1%, compared with 8.3% and 18.8% for CEA (≥7.0 and 3.9 ng/ml), 15.6% and 18.8% for CA 19-9 (≥37 and 26.7 ng/ml), 28.1% and 9.6% for CA 72-4 (≥4.0 and 13 ng/ml) and 7.3% and 7.3% for NSE (≥14.7 and 15.0 ng/ml) in the initial staging of primary SC. The area under the curve (AUC) for CYFRA 21-1, with a value of 0.978 (95% confidence interval, 0.964-0.991) was comparatively the highest. Univariate analysis revealed significant relationships between tumor marker level and lymph node involvement, metastasis and staging with CYFRA 21-1, CA 72-4 and NSE. Conclusions: CYFRA 21-1 was the most sensitive tumor marker and showed the most powerful diagnostic performance among the five SC tumor markers. NSE and CA 72-4 are significantly related to lymph node involvement, metastasis or stage. Further evaluations are warranted to clarify the clinical usefulness and prognostic prediction of these markers in SC.

Keywords: Stomach cancer - CYFRA 21-1 - CA 72-4 - NSE - CA19-9 - CEA

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Introduction

Stomach cancer (SC) is one of meaningful common malignancies and was the third leading cause of cancer-related death in Korea in 2010 (Jung et al., 2013). Although overall survival of SC has been improving because of early diagnosis with more sophisticated endoscopy regimens and altered eating habits (Chen et al., 2014), SC remains a concern. In the United States, an estimated 21320 new cases were reported in 2012 and the advanced stage of SC carries a poor prognosis below 30% (Siegel et al., 2013).

Carcinoembryonic antigen (CEA) produced by normal colonic cells and colon cancer cells has been investigated in various tumors including gastrointestinal cancers (Moertel et al., 1986; Zhang et al., 2012; Qin et al., 2013). Although CEA is usually used in preoperative staging and postoperative follow-up (Koga et al., 1987; Kodera et al., 1996; Ikeguchi et al., 1997; Sisik et al., 2013), its confidence has not been identified because of low sensitivity and unexpected elevated levels associated with smoking and various benign gastrointestinal diseases.

Carbohydrate antigen (CA) 19-9 is present in patients with colon and pancreatic cancers, and is important in the oncogenesis of endothelial cells (Koprowski et al., 1981; Liu et al., 2012). In SC, CA 19-9 is generally used for preoperative staging and post-treatment follow-up alone or along with other tumor markers such as CEA. In addition, CA 19-9 is a marker of poor prognosis in SC (Ucar et al., 2008; Choi et al., 2013) and shows more effective prognostic potential compared to CEA (Kodera et al., 1996). However, the usefulness of CA 19-9 in pretreatment screening and follow-up is debatable (Kodama et al., 1995; Duraker and Celik, 2001; Ucar et al., 2008).

CA 72-4 was identified as a high molecular weight mucin-like glycoprotein complex and designated tumor associated antigen 72 (TAG-72) (Ikeguchi et al., 1997; Mattar et al., 2002; Ubukata et al., 2003). It has been detected in high levels in pancreas, stomach, colon and endometrial cancers. In SC, it has been implicated as a valuable tumor marker related to the prediction of

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prognosis at preoperative staging (Ikeguchi et al., 1997).

Neuron-specific enolase (NSE) is a glycolytic enzyme present as a soluble cerebral protein. It is elevated in neuroblastoma, non-small cell lung cancer (NSCLC), medullary thyroid cancer and melanoma (Zeltzer et al., 1986; Koenig et al., 2001). Although no report has ascribed a clinical role for NSE as a tumor marker in SC, considering diffuse type of SC applied by the classification of Lauren was reclassified as neuroendocrine carcinoma (Waldum et al., 1998), evaluation of clinical usefulness of NSE in SC deserves consideration.

CYFRA 21-1 is a polypeptide tumor marker that is also designated circulating cytokeratin-19 fragment, which is produced by almost all human cells (Wieskopf et al., 1995; Molina et al., 2003; Nakata et al., 2004). Although its diagnostic utility and prognostic relevance have been demonstrated in NSCLC, colorectal cancer, breast cancer and cervical cancer (Gaarenstroom et al., 1995; Wieskopf et al., 1995; Nakata et al., 2004; Lee, 2013), little is known of the efficacy of pretreatment CYFRA 21-1 and the connection between CYFRA 21-1 and other tumor markers or clinical parameters in SC.

The present study sought to determine the diagnostic sensitivity of each of five tumor markers alone and in combination, to investigate the relationship between these five tumor markers and clinicopathologic parameters and to evaluate receiver operating characteristic (ROC) curve analysis of multiple tumor markers in preoperative SC patients.

Materials and Methods

Patients

Between January 2012 and December 2013, 336 patients with new onset primary SC in our hospital were enrolled. Preoperative evaluation of five tumor markers (CYFRA 21-1, CEA, CA 19-9, CA 50-3 and NSE) was done in a part of these patients. Healthy controls consisted of healthcare patients and patients with benign gastric disease without no history of gastric cancer. Eligibility requirements included primary gastric cancer proven by surgical specimen except stage 4, no history of surgical or endoscopic procedure before enrolled into this study and pretreatment F18-fluorodeoxyglucose positron emission tomography/computed tomography (F18-FDG PET/CT). TNM staging was classified according to the American Joint Committee on Cancer (AJCC) 7th edition. SC was classified into early gastric cancer (EGC) and advanced gastric cancer (AGC) according to criteria of the Japanese Classification of Gastric Carcinoma (Japanese Gastric Cancer Association, 2011). In addition, blood levels of the five tumor markers were checked and collected from patients with benign gastric diseases to evaluate the diagnostic judgement of each markers. This study was approved by the institutional review board of our hospital.

CYFRA 21-1, CEA, CA 19-9 and CA 72-4 assay

Before surgical treatment, blood sample of each patient was obtained by venupuncture, separated by centrifugation at 2500 rpm for 8 minutes and stored at -70°C until further analysis. Serum CYFRA 21-1 and CA 72-4 (iZotope, Budafest, Hungary) were measured by a solid-phase immunoradiometric assay based on the two-site sandwich method. Measurements of serum CEA, NSE and CA 19-9 (CIS Biointernational, Gif Yvette, France) were done by the same method.

The upper cutoff values of CYFRA 21-1, CEA, CA 19-9, CA 72-4 and NSE were 2.0 ng/ml, 7.0 ng/ml, 38 ng/ml, 4 ng/ml and 14.7 ng/ml, respectively, according to manufacturer's recommendations.

F18-FDG PET/CT

All patients fasted for a minimum of 6 h prior to F18-FDG injections. All serum glucose concentrations were <150 mg/dl. Patients were encouraged to have adequate water intake (about 500 mm) just before F18-FDG PET/CT to evaluate distended state of stomach. F18-FDG (185-444 MBq) was injected 1 h before F18-FDG PET/CT scanning. Patients then rested in a quiet, dimmed room for 1 h. F18-FDG PET/CT studies were carried out with a Gemini TF 64 PET/CT system (Philips, Hamburg, Germany). For attenuation correction and anatomic information, a low-dose CT scan (50-70 mA, 100-140 kVp, 0.5-s tube rotation, 2 mm section thickness) was carried out from the base of the skull to the upper thigh. Instructions for breathing and positioning were given to patients before or, if necessary, during emission scanning. After CT scanning, emission data acquisition was carried out with same direction as CT in the three-dimensional mode. The emission scan time at each step was 1 min 30 s, and eight to 10 bed positions (field of view, 180 mm) were acquired. A three-dimensional iterative reconstruction algorithm was based on Astonish TF. Two board certified nuclear medicine physicians (JHL and SGP) interpreted all F18-FDG PET/CT images. A significant finding on the PET scan was considered positive when abnormal non-physiologic F18-FDG uptake was consistently identified with pathologically confirmed lesions on gastrofibroscopy in distended stomach. The standard uptake value (SUV) of F18-FDG was calculated based on body weight.

Statistical analyses

Statistical analyses were performed using SPSS (version 14.0.0; SPSS, Inc., Chicago, IL). To evaluate the differences of tumor markers between EGC, AGC and controls with benign gastric diseases, the Kruskal-Wallis with pairswise mann-whitney test was used. Receiver operating characteristic (ROC) curves were plotted for CYFRA 21-1, CEA, CA 19-9, CA 72-4 and NSE to assess their diagnostic performances in differentiating primary SC from benign diseases. By analyzing ROC curves, modified cutoff values were calculated to evaluate sensitivity and parallel test. The relationships between clinicopathlogic factors and multiple tumor markers were evaluated by univariate analysis and Spearman's rank correlation. p-values <0.05 were considered statistically significant in this present study.

Results

Patient characteristics

Among total patients with pathologically confirmed

SC, 96 patients [37 females and 59 males; age (mean±SD) 59.1±12.8 years; range 28-81] with simultaneous preoperative evaluation of the five tumor markers were enrolled in this study. Operation managements performed in our patients consisted of surgical methods (72, 75%) and endoscopical procedure (24, 25%). The control group comprised 187 patients with benign gastric disease including various gastritis, ulcer, benign tumors [41 females and 146 males; age (mean±SD) 52.6±13.4 years; range 25-87] for each tumor marker groups. Other characteristics of patients with SC are shown in Table 1.

Sensitivities of and relationship between CYFRA 21-1, CEA, CA 19-9, CA 72-4 and NSE in patients with primary SC

In addition to cutoff values recommended by manufacturers, the adjusted cutoff values (CYFRA 21-1, CEA, CA 19-9, CA 72-4 and NSE) were investigated with regard to 95% specificity in patients with benign gastric diseases; value derived from corresponding ROC curves was 1.2, 3.9, 26.7, 13.0 and 15.0 ng/ml, respectively. Table 2 shows the sensitivity results of CYFRA 21-1, CEA, CA 19-9, CA 72-4 and NSE in primary SC. The sensitivities of CYFRA 21-1 were better than other tumor markers. Even sensitivities of CYFRA 21-1 were little different from those of parallel test (50% *vs* 57.3% and 78.1% *vs* 81.3%). Table 3 demonstrates that there are comparable relationship of each tumor markers between EGC, AGC and benign controls. General trends of five tumor markers in our study showed that those of EGC or benign controls were lower than AGC. In cases of CYFRA 21-1, CA 72-4, NSE and CEA, except CA 19-9, significant differences between the three groups were found ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.01$, respectively).

Table 1. Patients Characteristics of Our Enrolled Stomach Cancer Patients

Primary Stomach Cancer	
Median, years (range)	59, (28~81 years)
Gender	
Male	59
Female	37
Histopathology	
Adenocarcinoma	75
Well-differentiated	10
Moderate-differentiated	35
Poorly differentiated	30
Signet ring cell carcinoma	16
Mucinous carcinoma	4
Neuroendocrine carcinoma	1
TNM Stage	
Stage 1	42
Stage 2	14
Stage 3	27
Stage 4	13
Levels of tumor markers (Median, range)	
CEA (ng/ml)	1.9, (0.2-1819.0)
CA 19-9 (ng/ml)	9.9, (0.2-2276.8)
CYFRA 21-1 (ng/ml)	2.4, (0.5-81.0)
CA 72-4 (ng/ml)	2.5, (1.6-609.3)
NSE (ng/ml)	6.5, (1.8-55.5)

Assay of ROC curves

ROC curves were estimated to compare the capability of the five markers to differentiate patients with SC and benign gastric diseases (Figure 1). The area under the curves (AUC) for CYFRA 21-1, with a value of 0.978 (95% confidence interval, 0.964-0.991) was higher than other 4 tumor markers. AUCs (95% CI) for CEA, CA 19-9, CA 72-4 and NSE were 0.623 (0.545-0.701), 0.519 (0.439-0.559), 0.716 (0.610-0.823) and 0.383 (0.298-0.469), separately.

Relationship between clinicopathological factors and multiple tumor markers

According to sex difference, cutoff value of 45-years and differentiation of adenocarcinoma, there were no significant differences among the five tumor markers in univariate analysis (Table 4). There are significant intergroup differences with regards to T status and Stage in CYFRA 21-1 and CA72-4. According to nodal involvements and existence of metastasis, significant changes of tumor markers were found in CYFRA 21-1, CA72-4 and NSE. Tumor size was significantly correlated with CYFRA 21-1 (rho: 0.380, $p<0.01$), CA

Table 2. Sensitivity Results of CEA, CA 19-9, CYFRA 21-1, CA 72-4 and NSE in Patients with Stomach Cancer

	CEA	CA 19-9	CYFRA 21-1	CA72-4	NSE	Parallel Test[a]
(A) Sensitivity	8.3% (8/96)	15.6% (15/96)	50.0% (48/96)	28.1% (27/96)	7.3% (7/96)	57.3% (55/96)
Recommeded Cutoff Value (ng/ml)	7	37	2	4	14.7	-
(B) Sensitivity	18.8% (18/96)	18.8% (18/96)	78.1% (75/96)	9.6%(10/96)	7.3% (7/96)	81.3% (78/96)
Adjusted Cutoff Value (ng/ml)	3.9	26.7	1.2	13	15	-

[a]Parallel test: Even if only one tumor maker among them was increased over cutoff value, this test could be considered as positive

Table 3. Comparitive Relationships of CEA, CA 19-9, CYFRA 21-1, CA 72-4 and NSE between Benign Gastric Disease, EGC and AGC

	BGD[a]	EGC[b]	AGC[c]	P (k-w test[d])	P (BGD *vs* EGC)[e]	P (EGC *vs* AGC)[e]
CEA	1.8±1.5	2.2±1.3	35.3±236.3	0.006	0.03	0.567
CA 19-9	10.3±11.6	12.9±20.1	110.9±382.1	0.284	0.792	0.225
CYFRA 21-1	0.4±0.4	2.4±2.0	6.8±13.7	< 0.001	< 0.001	0.006
CA 72-4	2.8±3.3	2.5±0.6	27.6±92.3	< 0.001	0.004	0.001
NSE	7.9±1.7	6.5±2.1	9.7±9.3	< 0.001	< 0.001	0.132

*[a]BGD: Benign gastric disease, [b]EGC: Early gastric cancer, [c]AGC: Advanced gastric cancer, [d]k-w test: Kruskal-wallis test, $p<0.05$, [e]Significant difference between two groups was analyzed by Pairwise mann-whitney test and p-value of less than 0.017 was considered statistically important

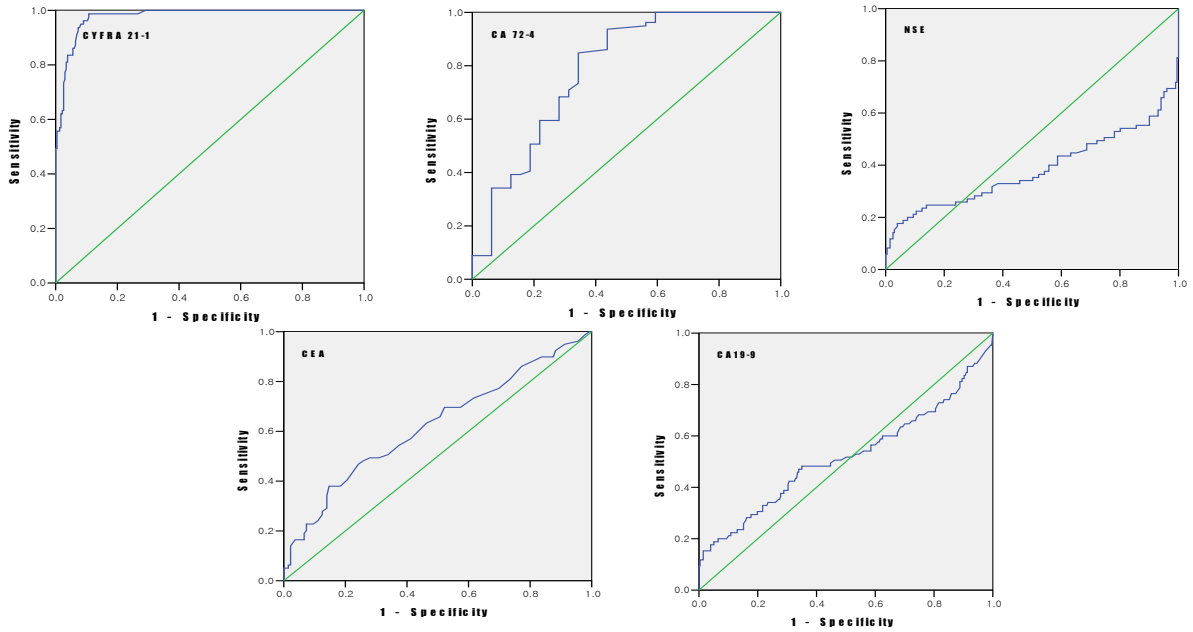

Figure 1. Analysis of Receiver-Operating Characteristic (ROC) Curves for CYFRA 21-1, CA 72-4, NSE, CEA and CA 19-9. The area under curve (AUC)s of CYFRA 21-1, CA 72-4, NSE, CEA and CA 19-9 were 0.978 (95% confidence interval, 0.964–0.991), 0.716 (0.610-0.823), 0.383 (0.298-0.469), 0.623 (0.545-0.701) and 0.519 (0.439-0.559), respectively

Table 4. Univariate analysis of CEA, CA 19-9, CYFRA 21-1, CA 72-4 and NSE According to Clinicopatholgical Variablesa

		CEA	P	CA19-9	P	CYFRA 21-1	P	CA72-4	P	NSE	P
T status	T 1&2	2.1±13	0.157	11.6±18.6	0.09	2.4±1.9	0.001	2.5±0.7	0.001	6.3±1.9	0.98
	T3	1.9±1.5		30.3±96.2		5.3±10.8		14.1±32.9		9.4±8.6	
	T4	6.4±1.1		73.5±98		10.8±19.6		24.9±74.4		11.9±12.4	
N status	Neg	2.3±1.4	0.961	12.4±19.2	0.39	2.5±1.7	0.018	2.8±1.6	0.001	6.1±1.8	<0.001
	Pos	3.8±7.7		47.8±95.5		6.6±14.1		17.9±54.7		10.5±10.1	
M status	Neg	2.3±2.1	0.034	22.6±59.8	0.035	3.1±2.3	0.001	5.2±14.8	<0.001	8.1±7.7	<0.001
	Pos	12.5±18.3		132.1±128.2		24.6±33.4		78.9±127.2		12.5±7.3	
Staging	I	2.2±1.2	0.325	13.9±20.5	0.157	2.3±1.6	0.005	2.9±3.7	<0.001	6.2±1.9	0.14
	II	1.7±0.9		15.8±25.1		3.3±2.1		4.2±2.6		10.8±9.7	
	III	2.9±3.4		42.7±104.4		3.5±2.7		9.4±26.7		9.6±11.3	
	IV	9.2±15.4		92.1±117.8		18.4±28		54.6±106.9		10.2±6.8	
Signet ring cell carcinoma											
	Neg	3.1±6.0	0.325	33.4±76.6	0.031	4.9±11.3	0.939	11.7±43.8	0.169	8.6±8.4	0.518
	Pos	3.2±3.8		17.6±41.9		3.2±2.3		5.4±5.8		6.9±2.6	

[a]Sex difference, cutoff value of 45 year old and differentiation of adenocarcinoma were not shown in this table

72-4 (rho:0.502, p<0.001) and SUV (rho: 0.462, p<0.001). Spearman correlative analysis between SUV and tumor markers showed only significant positive correlation between F18-FDG tumoral uptake and CA 72-4. In comparison between signet ring cell carcinoma and other SC histologic subtypes, only CA 19-9 showed significantly decreased level comparing that of other subtypes (p<0.05).

Discussion

We investigated the diagnostic performance of CYFRA 21-1, CA 72-4, CEA, NSE and CA 19-9 tumor markers using two divergent cutoff values and evaluated the relationship between clinicopathologic factors and the markers. As a way of using commercial recommended cutoff values and modified cutoff values assessed by ROC curves, the sensitivities of CYFRA 21-1 were higher than other four tumor markers, respectively (50% and 78%). In addition, CYFRA 21-1 revealed a distinctive potential to differentiate patients with EGC from controls with benign gastric diseases. When it comes to predicting diagnostic performance by analysis of ROC curves, CYFRA 21-1 showed most powerful result compared to the other tumor markers.

CYFRA 21-1 is a unique epitope from a polypeptide that is abundantly elaborated following cell death (Gaarenstroom et al., 1995; Wieskopf et al., 1995). Although CYFRA 21-1 was proven to be a valuable marker in staging and follow-up evaluation of various cancers, little has been known regarding a role in diagnosis and any association with clinicopathologic parameters of SC. Presently, CYFRA 21-1 used as commercial and adjusted cutoff displayed higher sensitivity than CEA or CA 72-4. Univariate analysis results of multiple tumor markers indicate that increasing staging and nodal involvement could have a tendency toward elevated CYFRA 21-1. Considering the powerful differentiation between EGC and patients with benign gastric diseases and results of

ROC curves analysis, CYFRA 21-1 could be a valuable tumor marker for SC. Among the five tumor markers of our study, adjusted cutoff level of CYFRA 21-1 could be utilized in preoperative screening, although CYFRA 21-1 was not specific to adenocarcinoma or signet ring cell carcinoma. Further studies involving many patients are needed to confirm the potential value as a screening tool.

CA 72-4 has been utilized to evaluate preoperative staging and diagnose recurrent SC. Elevated CA 72-4 can predict peritoneal metastasis and prognosis of operative treatment in AGC (Ikeguchi et al., 1997; Gartner et al., 1998). Our results showing significant discrimination according to tumor depth, nodal involvement and stage could support previous observations. In addition, only CA 72-4 has demonstrated a significant positive correlation with tumor FDG uptake, possibly reflecting poor prognosis (Yoshioka et al., 2003; Zhu et al., 2013) and there was little report regarding the relationship between FDG uptake of SC and tumor markers so far.

To the best of our knowledge, little is known of the clinical role of NSE in diagnosing SC and predicting the prognosis of SC. Although NSE was less powerful statistically than CYFRA 21-1, it was significantly associated with lymph nodal involvement status and metastasis ($p<0.001$, both). However, because the sensitivity of NSE was significantly lower than CYFRA 21-1 or CA 72-4 at both cutoff levels and that of EGC was more decreased than control groups ($p<0.001$), it may be inappropriate to evaluate the usefulness of pretreatment screening and clinically available cutoff value will be investigated.

CA 19-9 can be valuable in predicting prognosis and recurrence of SC after gastrectomy, and has a significant positive relationship with depth of invasion, nodal involvement and peritoneal metastasis (Gartner et al., 1998; Ucar et al., 2008; Lee et al., 2009; Choi et al., 2013). However, presently there was no significant connection between CA 19-9 and depth of invasion, nodal involvement, staging and differentiation except metastasis. In addition, CEA did not show any significant correlations with nodal involvement, depth of invasion and stage. But, although little is known regarding the frequency of use of multiple tumor markers in SC, CEA and CA 19-9 have been generally utilized in managing SC patients, compared to other markers. Judging from our results, customary routine use of these markers should be reconsidered. Although role of tumor marker has been limited to evaluate preoperative screening, considering sensitivity of CYFRA 21-1 was little different from that of parallel test and results of univariate analysis, it is suggested that clinical usefulness of CYFRA 21-1 could be better than other tumor markers.

There are a few limitations in this study. First, because of the follow-up was not long, detailed analyses like multivariate analysis using the cox proportional hazards method were not conducted. In addition, only a few tumor markers were analyzed. However, because these five markers are presently used in management of SC management, other than TPS or M30-antigen, the present results may have clinical applicability.

In conclusion, CYFRA 21-1 was most sensitive according to recommended and adjusted cutoff values, and produced the possible best diagnostic performance compared to other tumor markers, considering analysis of ROC curves. Since NSE has not been evaluated as completely as CEA and CA 19-9 concerning SC, further investigations will be needed to prove the clinical availability of this marker in SC. Finally, rather than customary use of CEA or CA19-9, it may be necessary to expand clinical application of other tumor markers, such as CYFRA 21-1, CA72-4 or NSE, in the evaluation of SC, considering our results.

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