RESEARCH ARTICLE

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

Hee Keun Gwak¹, Jai Hyuen Lee²*, Seok Gun Park²

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

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; Ubakata 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
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 neuroblastoima, 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 medical procedures, no history of cancer or tumors, no history of cardiovascular, pulmonary, neurological or other diseases that may affect the results. All F18-FDG PET/CT images. A significant finding on the PET scan was considered positive when abnormal non-physiologic uptake in the stomach was observed. The standard uptake value (SUV) 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 patients with benign gastric diseases, the Kruskal-Wallis test with pair-wise Mann-Whitney 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 clinicopathologic 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 15.0ng/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).

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 | CA 72-4 | NSE | Parallel Test |
|----------------------------------|-------|-------|-------|-------|-------|
| (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) |
| Recommended Cutoff Value (ng/ml) | 9.9 | 2.4 | 2.5 | 6.5 | - |
| (B) Sensitivity | 18.8% (18/96) | 18.8% (18/96) | 78.1% (75/96) | 9.6% (9/96) | 7.3% (7/96) | 81.3% (78/96) |
| Adjusted Cutoff Value (ng/ml) | 3.9 | 26.7 | 1.2 | 13 | - |

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

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

| BGD* | EGC* | AGC* | P (k-w test) | P (BGD vs EGC)* | P (EGC vs AGC)* |
|------|------|------|-------------|----------------|----------------|
| CEA 1.8±1.5 | 2.2±1.3 | 2.7±1.5 | 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 | 6.2±2.1 | 9.7±9.3 | <0.001 | <0.001 | 0.132 |

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

|        | 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 | 0.001 | 5.3±10.8 | 0.001 | 14.1±32.9 | 0.001 | 9.4±8.6 |
| T4     | 6.4±1.1 | 73.5±98 | 10.8±19.6 | 0.001 | 24.9±74.4 | 0.001 | 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 | 0.001 | 17.9±54.7 | 0.001 | 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 | 0.001 | 78.9±127.2 | 0.001 | 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 | 0.005 | 4.2±2.6 | 0.005 | 10.8±9.7 |
| III    | 2.9±3.4 | 42.7±104.4 | 3.5±2.7 | 0.005 | 9.4±26.7 | 0.005 | 9.6±11.3 |
| IV     | 9.2±15.4 | 92.1±117.8 | 18.4±28 | 0.001 | 54.6±106.9 | 0.001 | 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 | 0.005 | 5.4±5.8 | 0.005 | 6.9±2.6 |

*aSex difference, cutoff value of 45 year old and differentiation of adenocarcinoma were not shown in this table*
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.

Acknowledgements
The present research was conducted by the research fund of Dankook University in 2013

References
Chen XJ, Li N, Huang YD, et al (2014). Factors for postoperative gallstone occurrence in patients with gastric cancer: a meta-analysis. Asian Pac J Cancer Prev, 15, 877-81.
Choi AR, Park JC, Kim J, et al (2013). High level of preoperative carbohydrate antigen 19-9 is a poor survival predictor in gastric cancer. World J Gastroenterol, 19, 5302-8.
Duraker N, Celik AN (2001). The prognostic significance of preoperative serum CA 19-9 in patients with resectable gastric carcinoma: comparison with CEA. J Surg Oncol, 76, 266-71.
Gaarentjost KN, Bonfrer JM, Kenter GG, et al (1995). Clinical value of pretreatment serum Cyfra 21-1, tissue polypeptide antigen, and squamous cell carcinoma antigen levels in patients with cervical cancer. Cancer, 76, 807-13.
Gartner U, Scheulen ME, Conradt C, et al (1998). Value of tumor-associated antigens CA 72-4 vs CEA and CA 19-9 in the follow-up after stomach cancer. Dtsch Med Wochenschr, 123, 69-73.
Ikeguchi M, Katano K, Saitou H, et al (1997). Pre-operative serum levels of CA72-4 in patients with gastric adenocarcinoma. Hepatogastroenterology, 44, 866-71.
Japanese Gastric Cancer Association (2011). Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer, 14, 101-12.
Jung KW, Won YJ, Hong BJ, et al (2013). Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res and Treat, 45,1-14.
Kodama I, Koufuku K, Kawabata S, et al (1995). The clinical efficacy of CA 72-4 as serum marker for gastric cancer in comparison with CA19-9 and CEA. Int Surg, 80, 45-8.
Kodera Y, Yamamura Y, Torii A, et al (1996). The prognostic value of preoperative serum levels of CEA and CA19-9 in patients with gastric cancer. Am J Gastroenterol, 91, 49-53.
Koenig A, Wojcieszyn J, Weeks BR, Modiano JF (2001). Expression of S100a, vimentin, NSE, and melan A/MART-1 in seven canine melanoma cells lines and twenty-nine retrospective cases of canine melanoma. Vet Pathol, 38, 427-35.
Koga T, Kano T, Souda K, Oka N, Inokuchi K(1987). The clinical usefulness of preoperative CEA determination in gastric cancer. Jpn J Surg, 17, 342-7.
Koprowski H, Herlyn M, Steplewski Z, Sears HF (1981). Specific antigen in serum of patients with colon carcinoma. Science, 212, 53-5.
Lee IK, Kim DH, Gorden DL, et al (2009). Prognostic value of CEA and CA 19-9 tumor markers combined with cytology

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014 4937

DOI:http://dx.doi.org/10.7314/APJCP.2014.15.12.4933
Evaluation of Multiple Tumor Markers for Stomach Cancer
from peritoneal fluid in colorectal cancer. *Ann Surg Oncol*, **16**, 861-70.

Lee JH (2013). Clinical usefulness of serum CYFRA 21-1 in patients with colorectal cancer. *Nucl Med Mol Imaging*, **47**, 181-7.

Liu X, Cai H, Wang Y (2012). Prognostic significance of tumor markers in T4a gastric cancer. *World J Surg Oncol*, **10**, 1-9.

Mattar R, Andrade CR, DiFavero GM, Gama-Rodrigues JJ, Laudanna AA (2002). Preoperative serum levels of CA 72-4, CEA, CA 19-9, and alpha-fetoprotein in patients with gastric cancer. *Rev Hosp Clin Fac Med Sao Paulo*, **57**, 89-92.

Moertel CG, O'Fallon JR, Go VL, O'Connell MJ, Thynne GS (1986). The preoperative carcinoembryonic antigen test in the diagnosis, staging, and prognosis of colorectal cancer. *Cancer*, **58**, 603-10.

Molina R, Filella X, Auge JM, et al (2003). Tumor markers (CEA, CA125, CYFRA21-1, SCC and NSE) in patients with non-small cell lung cancer as an aid in histological diagnosis and prognosis. Comparison with the main clinical and pathological prognostic factors. *Tumour Biol*, **24**, 209-18.

Nakata B, Takashima T, Ogawa Y, Ishikawa T, Hirakawa K (2004). Serum CYFRA 21-1 (cytokeratin-19 fragments) is a useful tumour marker for detecting disease relapse and assessing treatment efficacy in breast cancer. *Br J Cancer*, **91**, 873-8.

Qin H, Qu LL, Liu H, Wang SS, Gao HJ (2013). Serum CEA level change and its significance before and after gefitinib therapy on patients with advanced non-small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 4205-8.

Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *CA: A Cancer J Clin*, **63**, 11-30.

Sisik A, Kaya M, Bas G, Basak F, Alimoglu O (2013). CEA and CA 19-9 are still valuable markers for the prognosis of colorectal and gastric cancer patients. *Asian Pac J Cancer Prev*, **14**, 4289-94.

Ubukata H, Katano M, Motohashi G, et al (2003). Evaluation of CA72-4 as a tumor marker in patients with gastric cancer. *Gan To Kagaku Ryoho*, **30**, 1821-4.

Ucar E, Semerci E, Ustun H, et al (2008). Prognostic value of preoperative CEA, CA 19-9, CA 72-4, and AFP levels in gastric cancer. *Adv Ther*, **25**, 1075-84.

Waldum HL, Aase S, Kvetnoi I, et al (1998). Neuroendocrine differentiation in human gastric carcinoma. *Cancer*, **83**, 435-44.

Wieskopf B, Demangeat C, Purohit A, et al (1995). Cyfra 21-1 as a biologic marker of non-small cell lung cancer. Evaluation of sensitivity, specificity, and prognostic role. *Chest*, **108**, 163-9.

Yoshioka T, Yamaguchi K, Kubota K, et al (2003). Evaluation of 18F-FDG PET in patients with advanced, metastatic, or recurrent gastric cancer. *J Nucl Med*, **44**, 690-9.

Zeltzer PM, Marangos PJ, Evans AE, Schneider SL (1986). Serum neuron-specific enolase in children with neuroblastoma. Relationship to stage and disease course. *Cancer*, **57**, 1230-4.

Zhang HQ, Wang RB, Yan HJ, et al (2012). Prognostic significance of CYFRA21-1, CEA and hemoglobin in patients with esophageal squamous cancer undergoing concurrent chemoradiotherapy. *Asian Pac J Cancer Prev*, **13**, 199-203.

Zhu SJ, Zhang Y, Yu YH, et al (2013). FDG PET-CT in non-small cell lung cancer: relationship between primary tumor fdg uptake and extensional or metastatic potential. *Asian Pac J Cancer Prev*, **14**, 2925-29.