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Original Article

Comparison of serum cytokeratin-18, CEA and CA 19-9 levels in esophageal and gastric cancers

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Abstract. The aim of this study was to determine clinical value of alone and combined use of serum cytokeratin (CK)-18, carcinoembryonic antigen (CEA) and CA 19-9 in esophageal squamous cell carcinoma and gastric adenocarcinoma. Serum tumor markers were measured in 60 patients who had esophageal squamous cell carcinoma or gastric adenocarcinoma. Thirty healthy subjects served as controls. In patients with gastric adecarcinoma serum CK-18 levels were significantly increased compared to both esophageal squamus cell carcinoma and control groups ($p<0.01$, $p<0,05$ respectively). But there was no significant difference in CK-18 levels between esophageal squamous cell carcinoma patients and healthy subjects ($p>0.05$). On the other hand, serum CEA and CA 19-9 levels did not differ between groups ($p>0.05$). The sensitivity of serum CK-18, CEA and CA19- 9 in esophageal squamous cell carcinoma were 53%, 70% and 66%, respectively. For gastric adenocarcinoma, the sensitivity of each tumor marker was similar 70%, 70% and 70%, respectively. CK-18/CA19-9 combination in the esophageal (83%) and gastric carcinomas (93%) were found to be more sensitive than other tumor markers when these markers were evaluated in combination.

CEA exhibited the highest sensitivity for esophageal squamous cell carcinoma compared to CK-18, and CA19-9. However, the sensitivity of all tumor markers in gastric adenocarcinoma were similar. The combination of CK-18 and CA19-9 could increase the diagnostic sensitivity in esophageal and gastric carcinomas.

Keywords: Esophageal carcinoma, gastric carcinoma, cytokeratin-18, CEA, CA19-9

1. Introduction

Gastrointestinal system (GIS) cancers are one of the major causes of malignancy-related deaths (1). Despite the decreasing incidence of gastric cancer in last decades mortality burden remains high. 5-year survival rate of patients with gastric cancer has not changed in the last 30 years, and many patients are still diagnosed at an advanced stage (2,3). Esophageal cancer is the ninth most common malignancy in the world with the highest incidence seen in developing countries. Its unique epidemiologic characteristics, high mortality, and increasing incidence have triggered significant research in many areas (4). The diagnosis of most of upper GIS cancers is made in the later stages of the disease when curative treatment is not possible. A diagnosis to be made in the earlier stage would be useful on the part of the patients in terms of reducing mortality and morbidity (2) Tumor markers are potentially useful in screening for cancer, monitoring the course of the disease, and detecting the relaps or recurrence after the treatment (5). Unfortunately, no tumor marker with high specificity and sensitivity could become a routine diagnostic or screening tool for upper gastrointestinal malignancies (6, 7). The advantage of combined use of multiple tumor markers is under debate for patients with gastrointestinal tumors. In clinical practice tumor markers such as CEA, CA19-9, CA 242 and CA 72-4 are commonly used for screening of gastrointestinal malignancies (8). The CEA, the wellacknowledged tumor-associated antigen of colon cancer was also described as a prognostic marker in patients with advanced gastric cancers (9). Serum CA19-9 was found to be better than CEA as a prognostic marker in patients with

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Table 1

Characteristics and Mean Serum CK-18, CEA, CA 19-9 Levels of The Groups.

	n	F/M	Age (X±SD)	CK-18* (X±SD)	CEA* (X±SD)	CA 19-9* (X±SD)
Esophageal squamous cell carcinoma	30	18/12	57,5±11	5,78±6,9	9,9±18	35,9±56
Gastric adenocarcinoma	30	19/11	56,9±8	11,50±13 ab	11,1±25	34,9±31
Healthy subjects	30	17/13	55,6±3	3,6±2	2,9±1	16,3±7

*Cut-off values of tumors markers; CK-18= 3,1 ng/mL, CEA= 2,62 ng/mL, CA 19-9= 16,5 U/mL ap< 0.05 group II vs group I, bp< 0.01 group II vs group III

gastric cancer (10). Cytokeratins, proteins of the intermediate filaments of epithelial cells, have been used as specific markers for tumor cells of epithelial origin (11). CK-18 is an intermediate-sized keratin-like filament characteristic for epithelial cells. Expression of the human CK-18 polypeptide was detected at the protein level in a large number of tumors (12). Cytokeratin–18 and two conventional biochemical markers, CEA and CA 19-9 were analysed in 90 patients with esophageal squamous cell carcinoma, gastric adenocarcinoma and healthy subjects. The aim of our study was to assess the clinical relevance of these three markers and to determine whether combined use of these markers could improve diagnostic sensitivity and specificity.

2. Material and method

A total of 60 patients, who had the diagnosis of esophageal squamous cell carcinoma and gastric adenocarcinoma through endoscopical and histopathological examination, were enrolled into the study. The patients were divided into two groups according to types of cancer: Group I was composed of 30 patients with squamous cell carcinoma (18 women, 12 men; mean age: 57.5±11); group II included 30 patients with gastric adenocarcinoma (8 men, 14 women; mean age: 56,9±8,8). The third group was composed of 30 healthy subjects (12 men, 8 women; mean age: 55,6±13,2) matched for age, sex and smoking habitus who were free of any gastric symptom or disease. The diagnosis of all the patients with cancer was confirmed by clinical, endoscopical and pathologic examination. Esophageal cancers were located in proximal (n=3), medial (n=8) or distal (n=19) thirds of esophagus. As for the gastric cancers 13 of them were localized in antrum, 11 in corpus and 6 in cardia. The histopathological examination revealed intestinal morphology in 27 patients and diffused-type adenocarcinoma in 3 patients according to Laurens' classification. Abdominal computed tomography (CT) scan was performed in all cases with esophageal and gastric carcinomas. In patients with esophageal cancer distant metastases were detected in liver in 3 patients and in lung in two at the time of diagnosis. In patients with gastric cancer, liver metastasis was found in 6 and peritoneal metastasis in 3, pancreatic metastasis in 2 and bilateral ovarian metastasis in 1 patient. Venous blood samples were drawn from each subject at the time of endoscopy. Blood was then centrifuged at 2000 rpm for 10 min in a refrigerated centrifuge to separate serum samples from the cells. All serum samples were stored at -70°C in plastic tubes until the analysis. Serum CK-18, CEA, CA19-9 levels were measured using the commercial IMMULITE Cytokeratin-18, CEA and CA19-9 kits, which were a solid-phase, two-site chemiluminescent immunometric assay.

All results were given as (mean±SD). The difference of serum levels of CK-18, CEA and CA19-9 among patients with esophageal squamous cell carcinoma and gastric adenocarcinoma were compared by one way-ANOVA model using Scheffe test. The difference was considered statistically significant if the *P* value was less than 0.05. The sensitivity of assay was defined as the number of true-positive assays divided by the total number of patients with cancer. Combined sensitivity of two tumor markers is defined as the percentage of patients in which the levels of at least one marker was higher than its cut-off value. The specificity of assay was defined as the number of true-negative assays divided by the total number of patients without cancer. A receiver operating characteristic (ROC) curve was constructed to decide the cut-off point and to assess the diagnostic accuracy of each tumor marker value for the diagnosis of

Table 2

Sensitivity, Specifities, Positive Predictive Value and Negative Predictive Value of CK-18, CEA, CA19-9 Used Alone and in Combination in Esophageal and Gastric Carcinomas

ParameterΦ	Esophageal squamous cell carcinoma					
	Positive	Negative	Sensitivity	Specificity	PPV*	NPV¶
	F/ M	F/ M	(%)	(%)	(%)	(%)
CK-18	9/7	9/5	53	57	55	54
CEA	11/10	7/2	70	60	63	67
CA 19-9	12/8	6/4	66	60	62	64
CK-18/ CEA	13/11	5/1	80	33	54	62
CK-18/ CA19-9	15/10	3/2	83	50	62	75
CEA/ CA19-9	13/11	5/1	80	33	54	62
CK-18/CEA/ CA19-9	15/11	3/1	86	30	55	69
			Gastric adenocarcinoma			
CK-18	14/7	5/4	70	57	62	65
CEA	12/9	7/2	70	60	63	67
CA 19-9	14/7	5/4	70	60	63	66
CK-18/ CEA	17/10	2/1	90	33	57	76
CK-18/ CA19-9	18/10	1/1	93	50	65	88
CEA/ CA19-9	17/10	2/1	90	30	56	75

Φ Cut-off values of tumors markers; CK-18= 3,1 ng/mL, CEA= 2,52 ng/mL, CA19-9= 16,5 U/mL
* Positive predictive value
¶ Negative predictive value

esophageal and gastric carcinoma. The predictive value of a positive assay was defined as the number of true-positive assays divided by the total number of positive assays. The predictive value of a negative assay was defined percentage of true-negative assays among all negative assays. The diagnostic efficiency was defined as the number of true-positive plus true-negative assays divided by the total number of patients with and without cancer.

3. Results

The difference in terms of age and gender distribution between the groups of cancer and healthy subjects were not found to be statistically significant ($p>0.05$). The mean serum levels of tumor markers were shown in Table 1. Using ROC curve (Figure 1), the cut-off value for serum CK-18, CEA and CA19-9 in esophageal squamous cell carcinoma and gastric adenocarcinoma were determined to be 3.1 ng/mL, 2.52 ng/mL and 16.5 U/mL, respectively. The cut-off values for tumor markers were same in esophageal and gastric cancer. Serum CK-18 values were found to be above the cutoff value of 3.1 ng/mL in 16 (53 %) of the patients with esophageal squamous cell carcinoma, 21 (70%) of the patients with gastric adenocarcinoma, and 13 (43%) of the controls. Serum CEA values were found to be above the cut-off value of 2.52 ng/mL in 21 (70%) of the patients with esophageal squamous cell carcinoma, 21 (70%) of the patients with gastric adenocarcinoma and 11 (36%) of the controls. Serum CA 19-9 values were found to be above the cut-off value of 16.5 U/mL, in 20 (66%) of the patients with esophageal squamous cell carcinoma, 21 (70%) of the patients with gastric adenocarcinoma, and 12 (40 %) of healthy subjects. The mean serum CK-18 levels in patients with esophageal and gastric carcinoma were higher than healthy subjects. The differences in serum CK-18 levels between gastric adenocarcinoma and healthy subjects ($p<0.01$) and between esophageal squamous cell carcinoma and gastric adenocarcinoma ($p<0.05$) were statistically significant. But there was no significant difference in CK-18 levels between esophageal squamous cell carcinoma and healthy subjects ($p>0.05$). The mean serum CEA and CA 19-9 levels in patients with esophageal squamous cell carcinoma and gastric adenocarcinoma were higher than healthy subjects. But there were no significant differences in serum CEA and CA 19-9 levels between the groups ($p>0.05$) (Table 1). The diagnostic power of serum CK-18, CEA and CA19-9 as a screening test for esophageal squamous cell carcinoma and gastric adenocarcinoma were assessed by ROC curve analysis. The ROC curve is drawn through points that represent different decision cut-off levels. The optimal combination of sensitivity and specificity for CK-18 were determined as 53% and 57% respectively in esophageal squamous cell adenocarcinoma, and 70% and 57% in gastric adenocarcinoma with a cut-off value of 3.1 ng/mL, respectively. In esophageal squamous cell carcinoma, the optimal combination of sensitivity and specificity for CEA were determined as 70% and 60% respectively, while for gastric adenocarcinoma 70% and 60%, for a cut-off value of 2.52 ng/mL. In esophageal squamous cell carcinoma, the optimal combination of sensitivity and specificity for CA19-9 were determined as 67% and 60% respectively, while for gastric adenocarcinoma 70% and 60%, for a cut-off value of 16.5 U/mL. CEA was more sensitive (70%) and specific (63%) than the other two markers in esophageal squamous cell carcinoma. However, among three markers no difference was found in terms of the sensitivity and specificity in gastric adenocarcinoma (Table 2)(Figure 1). Based on the results of the ROC curve, combined evaluation of two tumor markers increased the sensitivity. For example, the sensitivity of the combination of CK-18/CA19-9 was 83% in the esophageal squamous cell carcinoma and 93% in the gastric adenocarcinoma. Table 2 demonstrates the sensitivity and specificity values of such combinations.

4. Discussion

Serum tumor markers have been used in aiding the diagnosis of gastrointestinal cancers for a long time. Previous studies reported that the elevated serum values reflect the increased secretion of tumor antigens by tumor itself (13). However mild elevation of serum tumor marker levels in a number of early-stage cancers has always been difficult to justify as many benign pathologies may frequently cause such changes. The clinical use of tumor markers is much more beneficial in determination of prognosis, assessing response to treatment and detection of early recurrences (14). In our study, various tumor markers such as CK–18, CEA and CA19-9 have been investigated in the serum of esophageal squamous cell carcinoma and gastric adenocarcinoma, separately and in combination to define diagnostic sensitivity of these markers.

Cytokeratins are polypeptides that contribute to the formation of intermediate filaments forming the cytoskeleton, thus maintaining the structural integrity of the cell body cytokeratins are distributed in epithelial cells. At present 20 distinct cytokeratins have been identified in the cytoskeleton of epithelial tissues, and can be subdivided in two subfamilies; cytokeratin 9 to 20, acidic proteins with molecular masses of 40 to 65 kDa (type I), and cytokeratins 1 to 8,

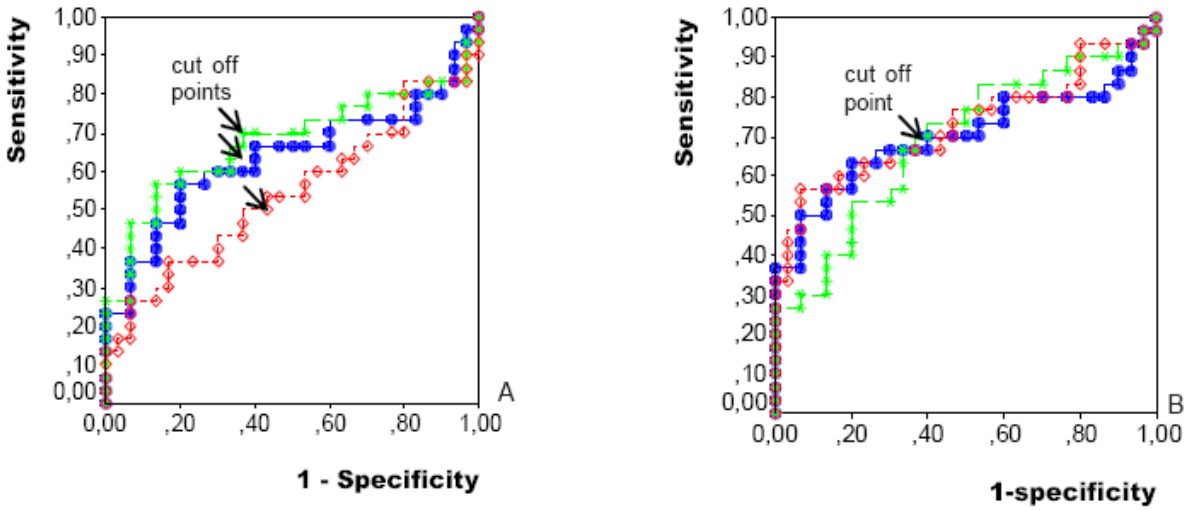

Figure 1. ROC curve of (—'—) cytokeratin–18, (—y—) CEA, (—q—) CA19-9 in esophageal squamous cell carcinoma (A) and gastric adenocarcinoma (B). The optimum true –positve and false positive rates are demonstrated using decision thresholds (arrows; cut-off points) of 3,1ng/mL for CK-18; 2,52 ng/mL for CEA and 16,5 U/mL for CA19-9.

neutral to basic proteins with molecular masses of 50 to 70 kDa (type II)(11,15). The differential expression of individual cytokeratins in various types of carcinomas makes them useful markers for histopathological carcinoma subtyping, providing relevant information concerning the differention and origin of carcinomas, especially when tumors first present as metastases (16). The most common cytokeratins in carcinoma are cytokeratin 7, 8, 18 and 19. They can be found intratumorally and in blood circulating as partially degraded complexes and can as such be used as tumor markers clinically (17). In adults, as it has been shown for other cytokeratins, CK-8, CK-19, and CK-18 is also over expressed in proliferating tissues such as endometriosis, liver cirrhosis, and malignant tumors. Soluble serum CK-18 has been proposed as a diagnostic tool in evaluating treatment response and early detection of relapse in a variety of human malignancies (18). It has been noted that the diagnostic values of CK-18 in patients with gastrointestinal tumours were higher. Few data exist on CK-18 in patients with gastric carcinomas (6). In our study, average serum CK-18 levels in patients with gastric carcinomas were found significantly higher than esophageal squamous cell carcinoma and healthy individuals. Regarding the cut-off values as 3.1 ng/mL, the sensitivity and specificity of CK-18 were determined as 53% and 57% for esophageal squamous cell carcinoma, 70% and 57% for gastric adenocarcinoma, respectively. The expression of CK-18 was detected in 75% of patients with esophageal squamous cell carcinomas (19). In another study, Kornec et al (6) reported 75 % sensitivity of CK-18 in patients with gastric cancer, so it has been pointed out that CK-18 is a much more sensitive marker than CEA and CA 19-9 in gastric cancer. Our results were consistent with that of Kornec et al (6). CEA is one of the most reliable tumor-associated markers used for the detection of malignancy. Serum CEA levels are used for cancer detection, determination of cancer stage and recurrence, and evaluation of cancer therapy, especially in patients with colorectal cancer (7). There have been many studies of CEA in patients with gastric cancer, but the role of serum CEA determination in these patients is still controversial (10). This may be due, in part, to findings that serum CEA levels and positivity rates are lower in patients with esophageal and gastric cancers than in those with colorectal cancer (20,21). Marked elevation of CEA was found to be associated with signet ring or poorly differentiated gastric carcinoma in the absence of liver metastasis (9). CEA has been reported to be beneficial in determining the relapses and the follow up of the responses to the treatment of the patients with gastric and esophageal cancers (22). In our study, regarding the cut-off values as 2.52 ng/mL, serum CEA levels were found to be higher in 70% cases with esophageal and gastric carcinomas, respectively. Gion et al (23) reported that CEA was positive in 27% of the patients with esophageal cancers. In the same study, it has been reported that the positivity rate of CEA was correlated with the stage of the disease. In another study CEA was found to be positive in 39% of cases with esophageal cancers (24). Elevated serum levels of CEA were shown to be positive in 14%-58% of gastric cancer patients

(24,25). Ychou et al (25) found that the sensitivity of CEA was 75% in 52 patients with gastric adenocarcinoma. Victorzon et al (21) reported that the sensitivity of CEA was 30-64% in patients with gastric cancers and its specificity was 67-73%. Koga et al (26) found that the sensitivity of CEA was 20 % in 468 cases with gastric cancer. In another study, CEA was found to be increasing in 14- 29% of localized cases and in 85% of cases with metastasis (27). Our results was consistent with that of Ychou et al (25). Besides being a marker closely associated with pancreatic cancer, CA19- 9 is also an adhesion molecule expressed on vascular endothelium (28). CA19-9 can be positive in colorectal, breast and liver cancers as well as in pancreas cancers (29). Serum CA19-9 was raised not only by tumors itselfs but also by infection (30). In our study, regarding the cut-off values as 16.5 U/mL, among the cases with esophageal and gastric carcinomas, serum CA19-9 levels were found to be higher in 66% and 70%, respectively. Our findings were relatively higher than those reported in literature. Gion et al (23) found that CA19-9 was positive in 13% of esophageal cancers and in 16% of gastric cancers. In another study the sensitivity of CA19-9 in gastric cancers was reported to be 30% and the specificity 54% (31). The positiveness of CA19-9 shows a correlation with the depth of tumor, its magnitude, and its metastasis to various organs and tissues (32). Although CA19-9 in gastric carcinoma is a better prognostic factor than CEA, the diagnostic value of such a tumor marker is limited (10,32). Both tumor markers shows a peak increase in those patients with hepatic metastasis. It is supposed that the decrease of hepatic elimination of CEA and CA19-9 plays a role in elevation of serum level of tumor markers in hepatic metastasis (33). The serum CA19-9 and CEA levels in two of our cases with gastric cancers with liver metastasis were found to be coherently higher, resembling those data in the literature. In the same way, serum CA19-9 levels were higher in two of our gastric cancer cases with pancreas metastasis. In order to enhance the sensitivity it is helpful to combine two assays together (7). In our study, the combination of CK-18 and CA19-9 could increase the sensitivity to 70% in esophageal carcinoma and 83% in gastric carcinoma. The combined evaluation of the three markers (CK-18, CEA, CA19-9) in serum resulted in a significant increase in diagnostic sensitivity compared to the combination of two tumors markers. This finding confirms the results previously reported by other authors. Lopez et al (7) reported that the combined use of CA72-4, CEA and CA19-9 could be beneficial in the diagnosis of esophageal and gastric cancers. There are also literatures contradicting the above ones. Patai et al (34) reported that the combined use of CA19-9 and CEA could not increase the diagnostic sensitivity in gastrointestinal cancers. ROC plateaus provide a wide range of spectral view of all possible sensitivity and specificity values. The y-axis plots the true-positive rate (the sensitivity) and the x-axis plots false-positive rate (1-specificity). Every test can reach to a high sensitivity in one point, but obtaining minimal false positive results in this point is crucial. Higher sensitivity of the markers in our study may be attributable to selection of lower cut-off values in ROC curve when compared to these studies reporting low sensitivity as they used considerably higher cut-off values. The present study showed that CEA has a higher positivity rate for esophageal squamous cell carcinoma than CK-18 and CA19-9. However, CK-18, CEA and CA19-9 showed similar sensitivity for gastric adenocarcinoma. The combination of three markers could increase the sensitivity in esophageal and gastric carcinomas.

In conclusion, the results of our study indicated that serum CK-18 is not a much more sensitive marker than CEA and CA19-9 in esophageal and gastric carcinomas. The combination of CK-18 and any other tumor marker would be more predictive since the different markers may act in a complementary fashion and provide a better clinical picture. In general terms, although most tumor markers are not satisfactory in the diagnosis of malignancy so far, tumor markers of esophageal and gastric cancer are more helpful in prognosis or recurrence, less so in early diagnosis. However, detailed studies are needed to prove the combined value of various markers in esophageal and gastric carcinoma.

References

1. Blot WJ. Esophageal cancer trends and risk factors. Semin Oncol 1994; 21: 403-10.
2. Coombes RC, Powels TJ. Tumour markers in the management of human cancer. In: Deeley TJ, editor. Topical Reviews in Radiotherapy and Oncology. Bristol: Wright PGS, 1982:39.
3. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg 1993; 218: 583-92.
4. Day NE, Varghese C. Oesophageal cancer. Cancer surv 1994; 20:43-54.
5. Mandorwski S, Lourenco LG, Forones NM. CA72-4 and CEA in serum and peritoneal washing in gastric cancer. Arq Gastroenterol 2002; 39:17-21.

6. Kornek G, Schenk T, Raderer M, Djavarnmad M, Scheithauer W. Tissue polypeptide specific antigen in monitoring palliative treatment response of patients with gastrointestinal tumours. Br J Cancer 1995; 71: 182-5.
7. Lopez JB, Royan GP, Lakhwani MN, Mahadaven M, Timor J. CA72-4 compared with CEA and CA19-9 as a marker of some gastrointestinal malignancies. Int J Biol Markers 1999; 14: 172-7.
8. Carpelan-Holmstrom M, Louhimo J, Stenman UH, Alfthan H, Haglund C. CEA, CA19-9 and CA72-4 improve the diagnostic accuracy in gastrointestinal cancers. Anticancer Res 2002; 22: 2311-6.
9. Horie Y, Miura K, Matsui K. Marked elevation of plasma carcinoembriyonic antigen and stomach carcinoma. Cancer 1996; 77: 1991-7.
10. Kodera Y, Yamamura Y, Torii A, et al. The prognostic value of preoperative serum levels of CEA and CA19-9 in patient with gastric cancer. Am J Gastroenterol 1996; 91: 49-53.
11. Moll R, Franke WW, Schiller DL, Geiger B, Krepler R. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 1982; 31:11-24.
12. Tschentscher P, Wagenera C, Neumaier M. Sensitive and specific cytokeratin 18 reverse transcription-polymerase chain reaction that excludes amplification of processed pseudogenes from contaminating genomic DNA. Clinical Chemistry. 1997; 43: 2244-50.
13. Pasanen PA, Eskelinen M, Partanen K, Pikkarainen P, Pentilla I, Alhava E. Clinical value of serum tumour markers CEA, CA50, and CA242 in distinction between malignant versus benign disease causing jaundice and cholestasis; results from a prospective study. Anticancer Res1992; 12: 1689-94.
14. Bunn PA, Cohen MI, Widerlite L, Nugent JL, Matthews MJ, Minna JD. Simultaneus and plasma immunoreactive CEA in 108 patients undergoing gastroscopy. Gastroenterology 1979; 76: 734-41.
15. Ridlander L, Zeigler E, Bergman T, et al. Molecular characterization of a tissue-polipeptide-specific-antigen epitop and its relationship to human cytokeratin 18. Eur J Biochem 1996; 241: 309-15.
16. Moll R. Cytokeratins in histological diagnosis of malignant tumors. Int J Biol Markers 1994; 912: 63-9.
17. 17- Sudstom BE, Stigbrant TI. Cytokeratins and tissu polipeptide antigen. nt J Biol Markers 1994; 9: 102-8.
18. Bonfrer JM, Groeneveld EM, Korse CM, van Dalen A, Oomen LC, Ivanyi D. Monoclonal antibody M3 used in TPSTM assay for the quantification of TPA recognizes keratin 18. Tumor Biol 1994; 15: 210-22.
19. Lam KY, Loke SL, Shen XC, Ma LT. Cytokeratin expression in non-neoplastic oesophageal epithelium and squamous cell carcinoma of the oesophagus. Virchows Arch 1995; 426:345-9.
20. Staab HJ, Anderer FA, Brummendorf T, Fisher R. Prognostic significance of preoperative carcinoembryonic antigen in stomach and colorectal cancer. Cancer Detect Prev 1983; 6: 149-53.
21. Victorzon M, Haglund C, Lundin J, Roberts PJ. A prognostic value of CA19-9 but not of CEA in patients with gastric cancer. Eur J Surg Oncol 1995; 21: 379-84.
22. Ial'chenko NA, Lagutin VD, Lavik NN, Musin II. The clinica information value of an immunoenzyme study of the tumor markers CA-19-9, CEA and AFP in cancer of the stomach, pancreas, colon and rectum. Vopr Onkol 1991; 37: 921-4.
23. Gion M, Tremolada C, Mione R, della Palma P, Dittadi R, Zari C, Nosadini A, et al. Tumor markers in serum of patients with primary squamous cell carcinoma of the esophagus. Tumor 1989; 75: 489-93.
24. Tachibana M, Takemoto Y, Nakashima Y, Kinugasa S, Kotoh T, Dhar DK, at al. Serum carcinoembryonic antigen as a prognostic factor in resectable gastric cancer. J Am Coll Surg 1998; 187: 64-8.
25. Ychou M, Duffour J, Kramar A, Gourgou S, Grenier J. Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. Dis Markers 2000;16: 105-10.
26. Koga T, Kano T, Souda K, Oka N, Inokuchi K, et al. The clinical usefulness of preoperative CEA determination in gastric cancer. Jpn J Surg 1987; 17: 342-7.
27. Bates SE, Longo DE. Use of serum tumor markers in cancer diagnosis and management. Semin Oncol 1987; 14: 102-138.
28. Berg el, Robinson MK, Manson O, et al. A carbohydrate domain common to both sialyl Le a and sialyl lex is recognized by the endothelial cell leukocyte adhesion molecule ELAM-1: J Biol Chem1991; 66: 1486-7.
29. Yoshikawa T, Nishida K, Tanigawa M, Fukumoto K, Kondo M. Carbohydrate antigenic determinant (CA 19-9) and other tumor markers in gastrointestinal malignancies. Digestion 1985; 31; 67-76.
30. Ker CG, Chen Js, Lee KT, Shee PC, Wu CC. Assesment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. J Gastro Hepatol 1991; 6: 505-8.
31. Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality. IARC Sci Publ 1993; 121: 806.
32. Marrelli D, Roviello F, De Stefano A, Farnetani M, Garosi L, Messano A, Pinto E. Prognostic significance of CEA, CA19-9 and CA72-4 preoperative serum levels in gastric carcinoma. Oncology 1999; 57: 55-62.
33. Fabris C, Bosso D, Meggiato T, Del Favero G, Piccoli A, Fogar P, et al. Different role of liver dysfunction and damage in increasing serum CA19-9, TPA and CEA in patients with pancreatic carcinoma. Int J Pancreatol 1990; 6: 1-8.
34. Patai A, Heber S, Dobronte Z, Kovacs LG. Diagnostic value of CA 19-9 and CEA in gastrointestinal pathology. Orv Hetil 1992; 133:1301-7.