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ORIGINAL ARTICLE

Do we really benefit from checking tumor markers in detecting recurrence in gastrointestinal cancer?

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Summary

Purpose: *To evaluate the role of tumor markers carcinoembryonic antigen (CEA) and CA 19.9 in the early detection of local or systemic recurrence in gastrointestinal malignancies.*

Patients and methods: *Twenty-six patients with operable gastrointestinal cancer, who had elevated levels of either CEA or CA 19.9 or both during the postoperative follow-up period were evaluated. Serum estimation of tumor markers were carried out at 3-month intervals and the imaging and endoscopic procedures were performed at 6-month intervals or when a patient had an elevated tumor marker during follow-up.*

Results: *The difference of mean serum levels of CA 19.9 but not of CEA was found to be statistically significant between the two groups of patients with or without radiographically / endoscopically evident recurrent disease ($p < 0.05$).*

Conclusion: *CA 19.9 was found to be a better, though not specific, indicator of recurrence. The relative small number of patients precludes reaching a firm conclusion. Further studies are needed to establish the role of these markers in determining early recurrence and their impact in overall survival.*

Key words: CA 19.9, CEA, gastrointestinal cancer, recurrence, tumor markers

Introduction

Cancers of the gastrointestinal tract constitute a most important cause of cancer-related mortality. Patients with unresectable advanced disease have poor prognosis, whereas the survival of patients at an early stage depends on the localization and grade of the primary tumor. In surgically resected gastrointestinal cancers, local or systemic recurrence usually occurs within a few years despite adjuvant postoperative therapy. Therefore, patients are followed up with imaging and endoscopic methods and/or measurements of serum tumor marker levels for early detection of recurrent disease so as to provide an earlier therapeutic intervention.

CEA is a protein-polysaccharide complex found in colorectal carcinomas and in normal fetal tissues [1]. Sensitive radioimmunoassays can detect increased levels in patients with gastrointestinal cancers, but the specificity is relatively low because positive tests also occur in heavy cigarette smokers, in patients with cirrhosis, ulcerative colitis and other cancers such as breast, lung, bladder, ovary and uterus [2]. Preoperative serum CEA levels have been shown to provide prognostic information for patients with potentially resectable gastric cancer [3]. Another widely used tumor antigen is the sialylated Lewis blood group antigen, carbohydrated antigen (CA) 19.9, which is detected by a monoclonal antibody. This antigen was

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initially found *in vitro* in cytosols of colorectal cancer cell lines and, thereafter, in various malignancies [4,5]. Although neither CA 19.9 nor CEA serum levels are useful for diagnosis, their utility has been demonstrated in monitoring the response to treatment and in patients in whom an eventual rise suggests recurrence and poor prognosis [3,6,7]. The latter is somehow controversial, since some other trials failed to show any survival benefit from serial measurements of CEA and CA19.9 [8-11].

The aim of our study was to evaluate the role of the tumor markers CEA and CA19.9 in the detection of local or systemic recurrence of gastrointestinal malignancies and to determine whether a correlation can be established between the serum levels of these markers and other radiologic and endoscopic findings used in follow-up for early detection of recurrence.

Patients and methods

Twelve male and 14 female patients with resected gastrointestinal cancers and elevated CEA and CA19.9 during their follow-up were included in the study. Their median age was 53 years (range 29-79 years). The characteristics of these patients are summarized in Table 1. The patients had elevations in serum levels of either CEA or CA19.9 or both. Physical examination and measurement of serum tumor marker levels were performed at 3-month intervals after the initial treatment. The serum level measurements of CEA and CA19.9 were performed by immunoassays with normal range of 0-5.2 ng/ml and 0-16 U/ml, respectively. The imaging and endoscopic procedures were performed at 6-month intervals or when the patient had an elevated tumor marker during follow-up.

All patients had histopathologically proven adenocarcinoma localized in different regions of the gastrointestinal tract: 13 patients had gastric cancer, 10 had colon cancer, and 3 had rectal cancer. All of the patients had received postoperative adjuvant therapy at Cerrahpasa Medical Faculty, University Hospital, Istanbul. Twenty-three patients had adjuvant chemotherapy and 3 patients with rectal cancer had received chemoradiotherapy within 4 to 6 weeks after curative surgery. Univariate and multivariate analyses were performed on SPSS 6.1 PC software.

Table 1. Patient characteristics (n=26)

Characteristic	*No. of patients (%)*
Sex	
male	12 (46.2)
female	14 (53.8)
Age (years)	
mean (range)	53 (29-79)
Site of primary disease	
stomach	13 (50.0)
colon	10 (38.5)
rectum	3 (11.5)
TNM stage	
I	2 (7.6)
II	12 (46.2)
III	12 (46.2)
Grade	
1	19 (73.1)
2	4 (15.4)
3	3 (11.5)
Adjuvant therapy	
chemotherapy	23 (88.5)
chemoradiotherapy	3 (11.5)

Results

During a median follow-up period of 58 months (range 18-72 months), 11 (42%) patients had no radiologic/endoscopic evidence of recurrent tumor despite elevated serum levels of tumor markers. Among them there were 7 patients with raised CEA, 2 with CA19.9 and 2 with both markers. The remaining 15 (58%) patients with elevated serum tumor markers were found to have either local or systemic recurrence detected by endoscopic or radiologic procedures or by surgical exploration.

The median time from curative surgery to the detection of elevation in serum CEA or CA19.9 levels or both was 10.5 months (range 1-36 months). This period was statistically not different (p= 0.44) between the groups of patients who had or had not radiologic and/or endoscopic evidence of recurrent disease (10 and 11 months, respectively). Recurrence sites and the diagnostic procedures used to determine recurrences are summarized in Table 2.

The mean CEA serum levels in patients without or with radiographically / endoscopically evident recurrent disease were 6 ng/ml (range 2-32 ng/ml) and 10.06 ng/ml (range 2-74 ng/ml), respectively. This was not statistically significant (p =0.207). On the contrary, the difference of mean serum levels of CA19.9 was found to be statistically significant between these two group of patients: 34.18 U/ml (range 1-92 U/ml) for the group without radiographically/endoscopically evident recurrent disease and 93.37 U/ml (range 1-500 U/ml) for the group with radiographically/endoscopically evident recurrent disease ($p < 0.05$).

Table 2. Sites and procedures used for detecting recurrence

	No. of patients
Patients with recurrence	15
Patients without recurrence	11
Sites of recurrence	
local	5
peritoneal	2
liver	2
gastric	1
pancreas	2
intestinal	1
lung	1
other	1
Diagnostic procedures for detecting recurrence	
CT	10
endoscopy	2
ultrasonography	1
ERCP	1
laparoscopy	1

Discussion

Early detection of recurrence in gastrointestinal cancers is difficult because these tumors are relatively inaccessible to detection by routine physical examination and localizing symptoms tend to occur late. Because metastatic disease is usually fatal, there has been a significant amount of effort focused on finding recurrent cancers before symptoms develop, at a stage when another curative resection is still possible. Tumor markers, chest x-rays, liver function tests, complete blood cell counts, fecal occult blood tests, computerized tomography and ultrasonography were all evaluated in this setting in the hopes of reducing the incidence of incurable metastatic disease. Since radiologic and endoscopic screening methods are relatively invasive and expensive, in patients undergoing curative surgery for gastrointestinal tumors regular postoperative serum CEA and or CA19.9 level measurements have been advocated as a means for providing early detection of recurrence [12]. Indeed several studies have been conducted to assess the utility of these tumor markers in gastrointestinal malignancies [8,13-16].

In our study, mean CEA serum levels in patients with or without radiographically /endoscopically evident recurrent disease was found not to be significantly different, whereas the difference of mean serum levels of CA19.9 was significantly different between these two groups of patients. Therefore CA 19.9 could serve as an early indicator of recurrent disease, even before radiological signs of recurrent disease manifest.

One study concluded that CEA is more sensitive than CA 19.9 in detecting recurrence in gastric and colorectal carcinoma, but that CA 19.9 was more specific. The investigators concluded that best results were obtained when both markers were used together [14]. A similar study evaluated serum levels of CA 19.9 and CEA in the follow-up of 370 patients with colorectal cancer and reported that the sensitivity of CA 19.9 in the early diagnosis of recurrence was much lower than that obtained for CEA [9].

Another study undertaken to determine if CEA level doubling time can predict the course of the disease in patients with adenocarcinoma of the gastrointestinal tract showed that there was a significant correlation between CEA doubling time and survival after the initial CEA increase in patients with recurrent gastric and colorectal carcinomas [17].

Another consideration is the diagnostic usefulness of each tumor marker, which is related to its sensitivity and specificity in making a diagnosis of cancer. Recently, CA 19.9 and CEA have been shown to function as sugar chain ligands of adhesive molecules, and their role in metastasis have begun to gain more importance on the basis that hematogenous metastasis is more likely to occur as their serum levels increase [18]. But it should also be noted that in the case of colorectal cancer for example, 30% of all colorectal cancer recurrences do not produce CEA and patients with normal preoperative CEA level may

Table 3. Serum levels of tumor markers

	Mean CEA level (ng / ml)		*Mean CA 19.9 level (U / ml)*	
All patients	8.4 (±8.17)		69.20 (±114.60)	
Patients without recurrence	6.0 (±6.69)	p=0.207	34.18 (±13.24)	p <0.05
Patients with recurrence	10.06 (±2.21)		93.37 (±145.34)	

Values are mean ± standard deviation

have an elevated CEA level at recurrence in about 40 % of the cases [19,20].

In summary, tumor markers could theoretically be used to determine early recurrent disease. A great number of studies exists, showing the role of the serum levels of these tumor markers in diagnosis, in determining prognosis and in monitoring response to treatment, however, their role in the early diagnosis of recurrence is still controversial [3,7,21,22].

In our study we found CA 19.9 to be a better, though not specific, indicator of recurrence. The relative small number of patients precludes reaching a firm conclusion. Further studies should be performed to determine if patients who are found to have a rise in CA 19.9 should undergo further diagnostic workup for possible salvage resection and/or chemotherapy, which might translate into improved survival.

References

1. Fletcher RH. Carcinoembryonic antigen. Ann Intern Med 1986; 104: 66-71.
2. Beers MH, Berkow R, Bogin RM, Fletcher AJ. Tumor Immunology. In: The Merck Manual of Diagnosis and Therapy (17th edn). Clays Ltd, England, 1999, pp 981-986.
3. Tachibana M, Takemoto Y, Nakashima Y et al. Serum carcinoembryonic antigen as a prognostic factor in resectable gastric cancer. J Am Coll Surg 1998; 187: 64-68.
4. Koprowski H, Steplewisky Z, Mitchell K, Herlyn D, Fulner P. Colorectal carcinoma antigens detected by hybridoma antibodies. Somat Cell Genet 1979; 5: 957-972.
5. Bates SE. Clinical applications of serum tumor markers. Ann Intern Med 1991; 115: 632-638.
6. Lorenzi M, Vindigni C, Minacci C et al. Histopathological and prognostic evaluation of immunohistochemical findings in colorectal cancer. Int J Biol Markers 1997; 12: 68-74.
7. Moertel CG, Fleming TR, McDonald JS. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA 1993; 270: 943-950.
8. Safi F, Kuhns V, Beger HG. Comparison of CA 72-4, CA19-9 and CEA in the diagnosis and monitoring of gastric cancer. Int J Biol Markers 1995; 10: 100-106.
9. Filella X, Molina R, Pique JM et al. Use of CA 19-9 in the early detection of recurrences in colorectal cancer: comparison with CEA. Tumor Biol 1994; 15: 1-6.
10. Fischbach W, Ritter P. How are tumor markers used in diagnosis and in aftercare of gastrointestinal cancers? Results of a nationwide German survey. Med Klin 1992; 87: 576-579.
11. Millat B, Borie F. Is it necessary to monitor patients surgically treated for colorectal cancer? J Chir 1998; 135: 177-181.
12. Cohen AM, Minsky BD, Schilsky RL. Cancer of the colon. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology. Philadelphia: Lippincott-Raven, 1997, pp 1144-1196.
13. Pectasides D, Mylonakis A, Kostopoulou M et al. CEA, CA 19-9 and CA-50 in monitoring gastric carcinoma. Am J Clin Oncol 1997; 20: 348-353.
14. Safi F, Bittner R, Roscher R, Kubel R, Beger HG. The value of CA 19-9 in gastric and colorectal carcinoma. Cancer Invest 1987; 5: 401-407.
15. Forones NM, Tanaka M. CEA and CA 19-9 as prognostic indexes in colorectal cancer. Hepatogastroenterology 1999; 46: 905-908.
16. McCall JL, Black RB, Rich CA et al. The value of serum carcinoembryonic antigen in predicting recurrent disease following curative resection of colorectal cancer. Dis Colon Rectum 1994; 37: 875-881.
17. Takesue, Inutsuka F, Nagahama S et al. Serum carcinoembryonic antigen doubling time in patients with recurrent gastrointestinal carcinoma and its relationship to tumor biology and life expectancy. Gan To Kagaku Ryoho 1998; 25 (Suppl 3): 464-468.
18. Takada A, Ohmori K, Yoneda T et al. Contributions of carbohydrate antigens sialyl Lewis A and sialyl Lewis X to adhesion of human cancer cells to vascular endothelium. Cancer Res 1993; 53: 354-361.
19. Safi F, Beyer HG. The value of follow-up after curative surgery of colorectal carcinoma. Cancer Detect Prev 1993; 17: 417-424.
20. Zeng Z, Cohen AM, Urmacher C. Usefulness of carcinoembryogenic antigen monitoring despite normal preoperative values in node positive colon cancer patients. Dis Colon rectum 1993; 36: 1063-1068.
21. Angel CA, Pratt CB, Rao BN et al. Carcinoembryonic antigen and carbohydrate 19-9 antigen as markers for colorectal carcinoma in children and adolescents. Cancer 1992; 69: 1487-1491.
22. Marrelli D, Roviello F, De Stefano et al. Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. Oncology 1999; 57: 55-62.