Role of CEA, TPA, and Ca 19-9 in the Early Detection of Localized and Diffuse Recurrent Rectal Cancer

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Sixty-six consecutive patients who underwent curative resection for rectal cancer were studied prospectively to evaluate the roles of sequential carcinoembryonic antigen (CEA), tissue plasminogen activator (TPA), and carcinomatous antigen 19-9 (Ca 19-9) determinations in the early diagnosis of resectable recurrences. Thirty-three recurrences were detected between 6 and 42 months. CEA, TPA, and Ca 19-9 showed a sensitivity of 72.7 percent, 78.8 percent, and 60.1 percent, respectively, and a specificity of 60.6 percent, 60.6 percent, and 87.9 percent, respectively. In 23 cases the rise in the value of CEA and/or TPA and/or Ca 19-9 was the first sign of recurrences, and the diagnosis was established later by clinical methods. In this group, the lead time was two months for liver metastases and four months for disseminated metastases. As far as the relationship between localization of recurrence and marker level increase is concerned, of 16 hepatic metastases CEA, TPA, and Ca 19-9 showed a sensitivity of 94 percent ($P < 0.05$), 69 percent, and 62 percent, respectively. Of six patients with local recurrences, CEA, TPA, and Ca 19-9 showed a sensitivity of 50 percent, 100 percent ($P < 0.05$), and 83.3 percent, respectively. Of three patients with peritoneal carcinomatosis, CEA, TPA ($P < 0.05$), and Ca 19-9 showed a sensitivity of 0 percent, 100 percent, and 0 percent, respectively. No significant differences were reported among the three markers according to multiple metastases and metachronous polyps. Fourteen patients (42.4 percent) underwent surgical treatment for recurrent disease, and eight of them (57 percent) showed a resectable disease, for a total resectability rate of 24.2 percent. The findings of our study indicate that a follow-up program based on CEA, TPA, and Ca 19-9 assays is related to an early diagnosis and a good resectability rate for both local and metastatic recurrences from rectal cancer. [Key words: CEA; TPA; Neoplastic marker; Rectal cancer]

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The concept of planned second-look laparotomy after curative resection for colorectal carcinoma was ideated by Wangesteen in 1951.[1] In their experience[2] over 13 years, of 153 "asymptomatic or symptomatic" patients with colon cancer who submitted to second-look laparotomies, 70 were found to have recurrent neoplasms, but only 5 were made free of disease; there were 11 operative deaths. Because of these results, this procedure was abandoned and the concept refused. However, the problem of recurrent disease was still present, with about half the patients treated for cure dying of recurrences within five years. The need for tests able to detect early and localized recurrence in the asymptomatic phase of the disease was pointed out by many authors.[3, 4]

Many examinations during these years claimed to be effective in detecting recurrent rectal cancer. These included history and physical examination, the stool guaiac test, barium enema, chest roentgenograms, liver scans, computerized tomography, and colonoscopy. All these tests present a low sensitivity and, in the majority of cases, are invasive; they could not be used routinely without great uneasiness for the patients. This problem would be worked out using neoplastic markers produced by the tumor and easily measurable in patients' serum.

An ideal tumor marker should have several characteristics: it should be present only in tumoral tissue and not in other tissues (normal or inflammatory); it should be tumor specific and present in all patients with this tumor; its concentration should be related to the stage of the neoplasm and also detectable in early stage; its concentration should be easily measurable in patient's serum; it should be produced by the metastasis of the neoplasm; and the rise in marker value in the presence of a metastases should be an early sign of relapse. The relationship between the tumor marker values and the course of the cancer is usually showed by a period in the disease in which the marker is elevated, then its values fall after operation and, during follow-up, rise in the presence of metastases. An ideal marker that presents all these char-

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acteristics does not exist.[5–8] However, use of more than one marker could supply these deficiencies.[9–11]

The goal of this article is to analyze the sensitivity and specificity of CEA, TPA, and Ca 19-9 and to evaluate their predictive value in detecting local and metastatic recurrences in patients already treated for cure of rectal cancer. The effect of this monitoring on the survival is also discussed.

MATERIALS AND METHODS

Sixty-six patients affected by rectal cancer and treated for cure from January 1983 to December 1985 were observed for a period ranging from 34 to 78 months (median, 64 months).

Patients undergoing palliative procedures or who submitted to adjuvant treatments (6 rectal cancer patients with synchronous metastatic disease involving less than 50 percent of the hepatic parenchyma, fully surgically resected) were excluded from this review. Thirty-nine patients were men and 27 were women, with a mean age of 62.3 years. Tumors were grouped according to Dukes classification: 6 tumors were Stage A, 32 were Stage B, 28 were Stage C. Twenty-six tumors were located in the upper third of the rectum, 24 in the middle third, and 16 in the lower third. All tumors were adenocarcinomas. Sixteen tumors were well differentiated (G1), 30 were moderately differentiated (G2), and 20 were undifferentiated (G3). Fifty-two anterior resections and 14 abdominoperineal amputations were carried out on the basis of tumor localization.

A limit of at least 2 cm of normal mucosa was spared in all cases. All patients underwent a preoperative and 10-day postoperative CEA, TPA, and Ca 19-9 assay. If there was no decrease of the postoperative assay to below the upper limit of normal, patients were excluded from the follow-up program. Patients were monitored with CEA, TPA, and Ca 19-9 by three-month assays. All surviving patients had at least six consecutive assays of the three markers with a maximum interval of four months between the assays. Fifty-four patients had a complete follow-up (from operation until death or January 1991) with the three markers.

CEA Assay

CEA was analyzed using a direct radioimmunologic method (CEA-PR; Sorin Biomedica). The upper limit of normal for this assay was 3 ng/ml. The lowest detectable level was 0 ng/ml.

TPA Assay

TPA was analyzed by the TPA-RIA system (AB Sangtec Medical), with an upper limit of normal of 85 U/liter. The lowest detectable level was 11 U/liter.

Ca 19-9 Assay

Ca 19-9 was analyzed using the Gica-RIA system (Sorin Biomedica), with an upper limit of normal of 25 U/liter. The lowest detectable level was 2 U/liter.

Defining the baseline as the lowest marker value recorded after operation, any elevation of one of the antigen levels greater than the limit defined by the between assay coefficient of variation (calculated on the basis of two standard deviations) was defined as significant, and the assay was repeated after 10 days. If the marker rise was confirmed, an abdominal or total body computed tomography (CT) scan, a chest x-ray examination, a bone scan, an endoscopy, and a clinical examination were performed. If recurrent neoplastic disease was confirmed by these examinations, the patient was evaluated for appropriate therapy, otherwise he/she was reviewed at the next scheduled clinic visit. According to the surgical management of metastatic disease, hepatic metastases were removed when they involved less than 25 percent of the liver, local recurrences were treated in each case when technically feasible, although diffuse peritoneal metastases contraindicate any surgical treatment. An exploratory laparotomy was performed when all three markers were elevated, even if recurrence was not confirmed by total body CT scan and clinical examinations. The follow-up schedule is shown in Table 1. Data were analyzed using the chi-squared test.

RESULTS

No patient was lost to the scheduled follow-up. Two patients died of nonneoplastic causes during follow-up. A total of 33 recurrences were found during follow-up. Ten recurrences were local (four cases in association with other metastases), all after an anterior resection, and none was from anastomotic origin. Twenty-five recurrences were met-

Table 1.
Follow-Up Schedule

	Months															
	3	6	9	12	15	18	21	24	30	33	36	39	42	48	54	60
CEA, TPA, Ca 19-9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Clinical examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Abdominal echography		+				+			+				+		+	
Chest x-ray		+				+			+				+		+	
Barium enema		+				+			+				+		+	
Colonoscopy				+				+			+			+		+
CT total body scan				+				+			+			+		+
Bone scan		+				+			+				+			

astatic. Recurrences were evident in the lung in 3 cases (all in association with other metastases), in the peritoneum in 10 cases (in 7 cases in association with other metastases), in the bones in 2 cases (all in association with other metastases), and in the liver in 21 patients (in 5 cases in association with other metastases). In 9 patients liver involvement was lower than 25 percent, in 6 cases it was between 25 and 50 percent, and in 6 cases liver involvement was higher than 50 percent. A total of 8 multiple metastases were demonstrated. Twenty-one adenomatous polyps were discovered and removed by operative colonoscopy. No metachronous tumor was found.

CEA and Recurrences

An increase in CEA levels confirmed in 2 consecutive serum samples within 10 days was considered a positive test, and this occurred in 37 patients. Of these, 24 had recurrence (positive predictive value of 64.9 percent). Nine patients with recurrence had normal CEA levels (test sensitivity 72.7 percent). There were 13 false positive CEA rises (test specificity 60.6 percent) (Table 2). None of these patients developed recurrence.

TPA and Recurrences

An increase in TPA levels confirmed in two consecutive serum samples within 10 days was considered a positive test, and this occurred in 39 patients. Of these, 24 had recurrence (positive predictive value of 66.7 percent). Seven patients with recurrence had normal CEA levels (test sensitivity 78.8 percent). There were 13 false positive CEA rises (test specificity 60.6 percent) (Table 2). None of these patients developed recurrence.

Table 2.
Characteristics of CEA, TPA, and Ca 19-9

	CEA (%)	TPA (%)	Ca 19-9 (%)
PPV*	64.9	66.7	83.3
NPV†	69.0	74.2	69.0
Sensitivity	72.7	78.8	60.1
Specificity	60.6	60.6	87.9
Accuracy	66.7	69.7	74.4

* PPV = positive predictive value.
† NPV = negative predictive value.

Ca 19-9 and Recurrences

An increase in Ca 19-9 levels confirmed in two consecutive serum samples within 10 days was considered a positive test; this occurred in 24 patients. Of these, 20 had recurrence (positive predictive value of 64.9 percent). Thirteen patients with recurrence had normal CEA levels (test sensitivity 60.7 percent). There were 4 false positive CEA rises (test specificity 87.9 percent) (Table 2). None of these patients developed recurrence.

As far as the relationship between localization of recurrence and marker level increase is concerned, of 16 hepatic metastases (the 5 hepatic metastases associated with other recurrences are excluded) CEA, TPA, and Ca 19-9 levels rose in 15, 11, and 10 cases, respectively (Table 3). No relationship was evidenced between marker levels increase and hepatic involvement (Table 4).

Of 6 patients with local recurrences CEA, TPA, and Ca 19-9 levels rose in 3, 6, and 5 cases respectively (Table 3). The two patients with both local and hepatic recurrence showed a simultaneous increase in all levels of the three markers. Of 3 patients with peritoneal carcinomatosis, CEA, TPA, and Ca 19-9 levels rose in 0, 3, and 0 cases, respectively (Table 3). Of 8 patients with multiple metas-

Table 3.
Relationship Between Marker Sensitivity and Localization of Metastases

	Hepatic (%)	Local (%)	Polyps (%)	Peritoneal (%)	Multiple (%)
CEA	93.7	50.0	19.0	0.0	75.0
TPA	68.7	100.0	38.1	100.0	75.0
Ca 19-9	62.5	83.3	23.8	0.0	62.5

Table 4.
Relationship Between Marker Sensitivity and Liver Involvement in 21 Hepatic Metastases*

	All (%)	<25% (%)	25–50% (%)	>50% (%)
CEA	84.2	88.9	55.6	55.6
TPA	57.9	33.3	66.7	66.7
Ca 19-9	52.6	33.3	50.0	66.7

* In 16 cases the liver was the only localization, and in 5 cases the liver was one of multiple localizations.

tases, CEA, TPA, and Ca 19-9 levels rose in 6, 6, and 5 cases, respectively (Table 3). Of 21 patients with adenomatous polyps of the colon, CEA, TPA, and Ca 19-9 levels rose in 4, 8, and 5 cases, respectively (Table 3). It should be pointed out that, of 9 recurrences misdiagnosed with CEA evaluation, 6 induced a rise in TPA value and 4 a rise in CA 19-9 level. These were in 3 cases disseminated peritoneal metastases, in 1 case a hepatic metastasis, in two cases multiple metastases, and in 3 cases local recurrences. Of 7 recurrences misdiagnosed with TPA evaluation, 4 induced a rise in CEA value and 3 a rise in CA 19-9 level. These were in 5 cases hepatic metastases and in 2 cases multiple metastases. Of 13 recurrences misdiagnosed with Ca 19-9 evaluation, 8 induced a rise in TPA value and 7 a rise in CEA level. These were in 3 cases disseminated peritoneal metastases, in 6 cases hepatic metastases, in 3 cases multiple metastases, and in 3 cases local recurrences. In 23 cases the rise in the value of CEA (19 cases) and/or TPA (19 cases) and/or Ca 19-9 (10 cases) was the first sign of recurrences, and the diagnosis was established afterward by clinical methods. In this group, the lead time for diagnosis of recurrence based on initial marker increase in comparison with routine clinical and instrumental follow-up was 2 months for liver metastases and 4 months for disseminated metastases.

In this study CEA appeared to have a better sensitivity than did TPA and Ca 19-9 in the detection of hepatic recurrences ($P < 0.05$). On the other hand, TPA demonstrated a better sensitivity than did CEA and Ca 19-9 in detecting localized and peritoneal recurrences ($P < 0.05$). Fourteen patients (42.4 percent) underwent surgical treatment for the recurrent disease, and eight of them (57 percent) showed a resectable disease, for a total resectability rate of 24.2 percent. Six regulated hepatic resections and two abdominoperineal amputations were performed. Six patients are still living after 11, 18, 23, 35, 43, and 55 months, respectively, from reoperation without evidence of neoplastic disease. Twenty-one patients died of disease; six patients are living with evidence of recurrent disease.

Only two patients with rectal cancer who presented recurrences had no increase in the value of one of the three markers. These patients showed in one case a solitary hepatic metastasis that was diagnosed by echotomography; in the other case, multiple pulmonary and hepatic recurrences were diagnosed by CT total body scan. In 18 patients without neoplastic recurrent disease there were two consecutive rises in one of the levels of the three markers, but none of these patients showed a simultaneous increase of the values of all three markers. None of these patients developed recurrences.

In two cases the rises of the levels of the three markers was the only sign of recurrent disease, and an exploratory celiotomy was performed. In one case the operation revealed a peritoneal carcinomatosis, and in the other case resectable hepatic recurrence was found. This patient is alive and disease free.

DISCUSSION

Marker titers have been used to predict or to detect recurrence in patients operated on for rectal cancer in many studies, and the majority of these used CEA as the only marker. Their findings showed for CEA measurements a sensitivity ranging between 60 and 95 percent, a lead time ranging between 2 and 10 months, a resectability rate ranging between 25 and 50 percent, and a 5-year survival rate ranging between 25 and 46 percent. The variability in these findings, in our opinion, might be attributable to: 1) The incidence of recurrences related to either to the presence in the study of more biologically advanced tumors or to a better accuracy of follow-up. 2) The use of different commercial kits with different specificity and sensitivity rates. The use of monoclonal CEA antibodies should elevate the sensitivity and specificity rates.

3) The execution of CEA determinations with different intervals. Best results were obtained in those studies in which CEA measurements were performed in monthly intervals.[12] 4) The limit above which CEA was considered "elevated" ranges in different studies from 3 ng/ml to 9 ng/ml. Martin *et al.*[12] developed a nomogram analysis based on the fact that follow-up assay should exceed the baseline (the postoperative CEA value) by more than two standard deviations, in case of tumor recurrence. Other investigators believe that this significant variation should be present in two consecutive measurements carried out 10 days from the each other, to exclude the presence of transient inflammatory disease.[11, 13–15] 5) The execution of second-look laparotomies only in the presence of significant CEA elevations, without waiting for clinical confirmation.

Studies have shown that the best results are obtained by reoperating immediately after the detection of a persistent rise in CEA.[13] On the other hand, this aggressive clinical approach leads to the execution of a number of meaningless second-look operations whose incidence ranges from 5 to 43 percent. In contrast, in the study of Attiyeh and Stearns,[16] of 37 second-look laparotomies performed in asymptomatic patients who had significant CEA elevations, resectable recurrences were found in 16 cases (43 percent), and no evidence of disease was found in 4 patients (11 percent). Lower CEA levels, shorter delays to surgery, and slower rates of CEA elevation were directly related to the resectability rate. Similar results were reported by Martin *et al.*[12] who found that of 146 asymptomatic patients re-explored on the basis of a rise in CEA, 55 percent had resectable recurrence. They performed seven negative laparotomies, although six of these patients subsequently developed recurrent tumors.

Minton and colleagues[17] reported 43 patients who underwent second-look surgery based just on an elevated CEA level and found recurrences in 92 percent of cases; they reported a 30 percent five-year survival rate. These data are discordant with those reported by Fucini *et al.*,[11] which abandoned the asymptomatic operations based solely on the elevation of the CEA after the first five failures (four negative laparotomies and one diffuse disease). In our study, in two cases in which the values of the three markers were elevated, even if recurrence was not confirmed by clinical or total body CT scan examinations, a "blind laparotomy" was performed. One disseminated and one resectable recurrence were found. On the other hand, execution of this procedure in the presence of the CEA rise alone would lead us to perform 13 unnecessary laparotomies, but no patient underwent a meaningless operation in our series. Nevertheless, even if CEA measurements are carefully performed, some authors claim that a CEA rise generally occurs late in the natural history of the disease, as an expression of a discrete amount of cancerous tissue,[11, 18, 19] and that disseminated small recurrences are not detected by serum CEA assays.[20]

Many studies combined CEA monitoring with other examinations during follow-up for colorectal cancer in diagnosis of early and localized recurrences amenable to surgical treatment. Deveney and Way[21] reported evidence in 23 patients with recurrence a sensitivity rate for CEA three-month assays of 61 percent, identical to the 61 percent for the CT scan six-month execution. On the other hand, three-month physical examination gave the first clue of recurrence in 48 percent of patients. In that study the resectability rate was 26 percent. In our study, the increase of one of the three markers was the first sign of recurrences in 79 percent of patients (with a 55 percent specific CEA rise), although clinical examination, CT scan, and chest x-ray were useful and aided in the determination of first recurrence in three cases (10 percent), in two (7 percent), and in one case (4 percent), respectively. Sugarbaker *et al.*[22] followed up 66 patients with high risk for recurrences using review of symptoms and physical examination, CEA assays, abdominal CT scan, full lung tomography, liver-spleen scan every three months, and they found that the series CEA values were positive in 81 percent of the patients with recurrent disease, and CT scan obtained a positive test result of 51.5 percent (17 of 33), with a site-specific positive finding of 85 percent (17 of 20). Furthermore, they found that a CEA rise was the first sign of recurrence in 67 percent of the patients, clinical examination in 21 percent, and CT scan in 6 percent of patients. In accord with Sugarbaker *et al.*,[22] we think that as soon as recurrent disease is suspected on the basis of an increase of a marker value, then CT scan, full lung tomography, hepatic echotomography, and bone scintigraphy are helpful during work-up to localize recurrence.

A few studies have analyzed the effectiveness of a follow-up based on the periodical evaluation of the three markers. Our findings are not completely

consistent with those reported by Fucini and colleagues,[11] who followed up 66 patients with colorectal cancer and found for CEA, TPA, and Ca 19-9 a sensitivity of 90 percent, 60 percent, and 20 percent and a specificity of 83 percent, 50 percent, and 90 percent, respectively. In our study, CEA revealed the lowest sensitivity and specificity (73 percent and 61 percent), TPA showed a better sensitivity and specificity (79 percent and 60 percent), and Ca 19-9 a higher sensitivity (60 percent) and the same specificity.

Furthermore, we demonstrated that TPA seems the most sensitive marker available for the detection of local recurrences from rectal cancer, although CEA showed a better specificity in the detection of hepatic metastases. However, the rise of Ca 19-9 was almost always related to the development of a recurrence.

CONCLUSION

Our study indicates that a rectal cancer follow-up based on the periodic evaluation of CEA, TPA, and Ca 19-9 is useful in early detection of recurrences and gives better results than does a follow-up based on CEA monitoring alone. Asymptomatic second-look surgery based on the increase of the values of the three markers improves the resectability rate and the five-year survival rate.

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