Unrecognized Value of Carcinoembryonic Antigen in Recurrent Rectal and Sigmoid Colon Cancer: Case Series

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ABSTRACT

Introduction: Carcinoembryonic antigen (CEA) surveillance is recommended in patients with colorectal cancer for detection of potentially resectable metastases. In patients with appropriate symptoms, a highly increased CEA concentration (> 5 times the upper limit of normal) is considered strongly suggestive of cancer. Despite the recognized value, the test is neither absolutely sensitive nor specific for recurrent cancer. Generally, a greater diagnostic value has been assigned to elevated CEA levels, most commonly greater than 5 ng/mL. Fluctuations within the established normal CEA range are not customarily analyzed.

Case Presentations: We report here on 11 patients (8 women, 3 men) who, during the postoperative follow-up period, received a diagnosis of recurrent cancer despite their CEA levels exhibiting very subtle increases. Our cohort shared several similar characteristics such as a nonsmoking status, younger age (median, 52 years at initial diagnosis), and exclusive localization of the cancer to the rectosigmoid region.

Discussion: This important clinical observation may expand a prognostic value of CEA in a certain category of patients with colorectal cancer.

INTRODUCTION

Carcinoembryonic antigen (CEA) surveillance is recommended in patients with colorectal cancer (CRC) for detection of potentially resectable metastases.[1,2] In patients with appropriate symptoms, a highly increased CEA concentration (> 5 times the upper limit of normal) is considered strongly suggestive of cancer.[3] Despite the recognized value, the test is neither absolutely sensitive nor specific for recurrent cancer. Generally, a greater diagnostic value has been assigned to elevated CEA levels, most often greater than 5 ng/mL. The fluctuations within the established normal CEA range are not customarily analyzed.

We describe 11 patients in whom recurrent CRC was diagnosed during postoperative follow-up despite their CEA levels exhibiting very subtle increases.

CASE PRESENTATIONS

From 2000 through 2016, a total of 11 patients in our department who were undergoing standard CRC surveillance according to the National Comprehensive Cancer Network guidelines[4] were identified and their medical records were reviewed. The cohort was selected on the basis of cancer recurrence in the setting of CEA levels that exhibited an incline but fell short of surpassing the upper limit of normal.

The relevant clinical data of the patients are presented in Table 1. Eight of the 11 patients were women, and the median age of the whole group was 52 years (range, 44-73 years; mean, 56 years). At the time of initial diagnosis, 1 patient had stage I, 4 patients had stage II, and 6 patients had stage III cancer. Only a single patient had a poorly differentiated adenocarcinoma, whereas most had moderately or well-differentiated tumors. The cancer was located in the rectum in 5 patients, in the sigmoid colon in 5 patients, and at the rectosigmoid junction in 1 patient. The recurrent cancer was confirmed by results of the biopsy of the suspicious lesion detected on computed tomography or positron emission tomography/computed tomography, or during the surgery. In 1 patient the biopsy was not technically feasible, so the recurrence was diagnosed on the basis of retroperitoneal fluorodeoxyglucose-avid lymph nodes (LNs) and CEA elevation, which was effectively treated with stereotactic radiosurgery. Seven patients had relapsed with a single metastasis: 4 in the lung, 1 in the liver, 1 in an abdominal LN, and 1 in a retroperitoneal LN. Four patients displayed multiple sites of recurrence, including the peritoneum (n = 1); the liver and colon (n = 1); the retroperitoneal, mediastinal, and supraclavicular LNs (n = 1); and the lung and brain (n = 1).

The serum CEA assay was performed according to an immunochemical automated analyzer (Abbott AxSym, Abbott Laboratories, North Chicago, IL) using a microparticle enzyme immunoassay with a normal range of equal to or below 5.0 ng/mL. The median preoperative CEA level (assessed in 9 of 11 patients) was 3.58 ng/mL (range, < 1.0 to 12.3 ng/mL), and the postoperative CEA was 1.03 ng/mL (range, < 1.0 ng/mL to 2.9 ng/mL). At the time of recurrence, the median CEA level was 2.97 ng/mL (range, 1.1 ng/mL to 4.8 ng/mL). In 1 patient (Table 1, Case 1), CEA demonstrated an abrupt, minuscule but perceptible increase above the level that had been remarkably stable over 5 years. Most patients displayed at least 3 steadily rising CEA values above the nadir over variable periods.

The median time to recurrence was 37.6 months (range, 19 to 65 months), with a median survival of 91.9 months (range, 41 to 162 months). Five of 11 patients died. The 6 patients who are alive have survived from 41 to 162 months (median, 83.8 months). The median time to recurrence in surviving patients varied from 19 to 66 months (median, 34.2 months).

DISCUSSION

Despite the lack of survival benefit, CEA surveillance has been recommended in the postoperative period to improve the

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detection of recurrent CRC, including those cancers that could be treated with curative intent. The accuracy of the test has been debated for years, prompting more sophisticated methods of CEA assessment such as CEA doubling time and CEA half-life.[5] In general, the higher the level of CEA, the higher the specificity of the test. Therefore, the studies have traditionally focused on the high-risk patients with elevated preoperative CEA (> 5 ng/mL) and, especially, patients with persistent CEA elevation after surgery.[6] An interpretation of the CEA levels is more problematic when the levels fluctuate in the normal or near-normal range, mostly for the following reasons: 1) the small variations are subject to oversight; 2) the minor fluctuations may be attributed to medical conditions other than cancer or to tobacco exposure, which may trigger minor but false CEA elevations[3]; and 3) CEA sensitivity and specificity can vary depending on the brand of assay used, so no uniform normal CEA values have been established. Even more important, up to 70% of CRC recurrences occur without CEA elevation (at normal CEA level).[7] In many such cases the serum CEA has no biological connection to the cancer because approximately 30% of all CRC recurrences do not produce CEA.[8] Despite all these challenges, a normal CEA level could still be a subtle marker of cancer recurrence, as was demonstrated in the study, with an upper limit of normal CEA of 10 ng/mL.[9]

We identified 11 patients with recurrent cancer whose CEA levels before the diagnosis demonstrated small elevations that were confined to the established normal limits. The interpretation of such narrow-range CEA fluctuations requires careful distinction from nonspecific, potentially false-positive deviations. For example, previous studies have seldom made a distinction between smokers and nonsmokers,[10] or men vs women, despite the proven differences in their CEA levels. According to our laboratory reference studies, the 90th percentile upper limit for smokers is 5.0 ng/mL and the 95th percentile for nonsmokers is 3.0 ng/mL. In a large reference study, the upper limits of the CEA assay for male smokers and nonsmokers were 6.2 and 3.4 ng/mL, respectively, and for female smokers and nonsmokers, 4.9 and 2.5 ng/mL, respectively.[11] Thus, smoking appears to almost double the serum concentration of CEA and may certainly confound the interpretation of the results. All our patients were nonsmokers at the time of evaluation. Four of 11, however, showed CEA greater than 3.0 ng/mL (upper level for nonsmokers). Additionally, none of our patients had conditions that potentially may result in nonspecific CEA elevation, including cirrhosis, hepatitis, biliary obstruction, pulmonary emphysema, diverticulitis, inflammatory bowel disease, peptic ulcer disease, or collagen vascular disease.[12]

Table 1. Characteristics of patients with colorectal cancer

Case	Sex	Age, y	Adenocarcinoma type	Stage	Location	Time to recurrence (mo)	Recurrence (location/no. of sites)	Carcinoembryonic antigen level (ng/mL)		
								Preoperative	Postoperative	At time of recurrence
1	F	69	Moderately/well differentiated	II	Sigmoid	65	Liver, colon/ multiple	Not done	< 1.0	1.1
2	F	73	Moderately differentiated	I	Rectal	36	Lung/single	1.9	1.3	3.5
3	F	50	Moderately/well differentiated	II	Rectal	28	Lung/single	3.7	< 1.0	3.5
4	F	59	Moderately/poorly differentiated	III	Sigmoid	30	Peritoneum/ multiple	Not done	< 1.0	2.8
5	F	70	Moderately differentiated	II	Sigmoid	42	Lung/single	6.3	< 1.0	1.8
6	F	53	Moderately differentiated	II	Rectosigmoid	45	Retroperitoneal, mediastinal, supraclavicular lymph nodes/ multiple	1.6	< 1.0	1.6
7	F	44	Moderately/well differentiated	III	Rectal	58	Lung, brain/ multiple	< 1.0	< 1.0	3.0
8	M	45	Poorly differentiated	III	Sigmoid	24	Abdominal lymph node/ single	2.5	1.4	4.8
9	M	50	Moderately/well differentiated	III	Sigmoid	19	Liver/single	1.6	1.1	4.5
10	F	52	Moderately differentiated	III	Rectal	31	Lung/single	12.3	1.6	2.5
11	M	52	Moderately differentiated	III	Rectal	36	Retroperitoneal lymph node/ single	1.8	2.9	3.6

The CEA levels in patients with CRC have rarely been studied in regard to the cancer location.[13] The most striking observation was that the cancers in our patients were localized exclusively to the rectal and sigmoid region. The cause of such a location clustering is unclear. It is plausible, however, that our cohort exemplifies a biologically distinct subcategory of CRC. For example, our patients have demonstrated more indolent than average cancer growth. Furthermore, 7 of 11 patients presented with oligometastatic recurrence, which is a recognized prerequisite of curability. The latter features could account for the lower, and stagnant, CEA levels in our patients (as well as a longer survival). The lower preoperative CEA levels have previously been linked to better outcomes. This was convincingly shown in both pulmonary[14,15] and liver[16] metastasectomy settings. Thus, the evidence suggests better outcomes when the cancer produces no or very small amounts of CEA.

Another distinguishing feature of our cohort was that it was nearly 10 years younger than a statistical median age for patients with rectal cancer.[17] Also, the prevalence of the female sex, which is a reverse of average statistics, may provide an additional clue for this cluster (target) population identification.

Although more intensive surveillance with CEA screening consistently results in an increased rate of curative-intent surgical treatment, the cure rate remains suboptimal, as no survival benefit has been demonstrated yet. To improve the validity of CEA screening, an individualized and perhaps selective measurement approach may be necessary. Our study could be a step in this direction.

Our collective data on patients with CRC for more than 6 years (2010-2015) yielded an estimated incidence of the cohort of 0.7%. (On average, 91 new patients were seen annually during this period.) The fact that our cohort represents only a small subset of the CRC population highlights the importance of rigorous identification of such patients. Despite the rare occurrence, such cases could be easily overlooked and thus their incidence underestimated.

CONCLUSION

The upward trend of postoperative CEA level even within the normal range may be clinically relevant and, given appropriate attention, potentially lifesaving. Our observations suggest that a correctly defined subset of patients with rectal and sigmoid cancers may constitute a target population requiring maximum vigilance and cautious interpretation of CEA trends within an established normal range.

Our findings have also exposed an important but elusive relevance of the patient's gender and tobacco use to the subtle postoperative CEA changes. Hopefully, the recognition of better-defined subcategories of patients with CRC as well as early intervention, before CEA levels become grossly abnormal, will expand a prognostic value of CEA and, ultimately, improve clinical outcomes. Although our study was small and included only 11 patients, it illustrates an important clinical observation that should be further evaluated in future studies. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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