Carcinoembryonic antigen screening: how far should we go?

Lim Y K, Kam M H, Eu K W

ABSTRACT

Introduction: The role of carcinoembryonic antigen (CEA) in screening has been previously investigated and found to be inefficient because of its low sensitivity and specificity. Nevertheless, it is still used as a tumour marker in health screening packages, often for asymptomatic patients. We aimed to review all asymptomatic patients who were referred to our department for raised CEA, to determine if this was indeed associated with significant pathology, and to what extent the asymptomatic patients should be investigated.

Methods: All patients with no gastrointestinal symptoms, and whose only indication for endoscopy was a raised CEA level, were entered into the study group. All the investigations were retrospectively reviewed and any pathology was noted.

Results: There were 217 asymptomatic patients who presented for endoscopy and further evaluation due to raised CEA, from December 1998 to August 2004. After the initial investigations, a total of 20 primary and eight metastatic cancers were found. The malignancies detected included 11 colorectal cancers, two stomach cancers, five lung cancers, one periampullary carcinoma and one ovarian teratoma. There were two cases of metastasis in the lungs and six with liver metastasis. In the subsequent median follow-up period of 13 (range 6–97) months, an additional 16 (7.4 percent) primary cancers were detected.

Conclusion: Asymptomatic average-risk patients who present with raised CEA should be investigated endoscopically and radiologically for commonly-associated cancers, and thereafter followed up for at least two years, as up to 7.4 percent present with a subsequent malignancy.

Keywords: cancer screening, carcinoembryonic antigen, colorectal cancer, tumour marker

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INTRODUCTION

Colorectal cancer is among the top three causes of cancer deaths in many developed countries. In Singapore, it has emerged as the most prevalent cancer for both genders combined, with a total of 6,101 reported cases in the Singapore Cancer Registry from January 1998 to December 2002.[1] Carcinoembryonic antigen (CEA), first described by Gold and Freeman in 1965, is a complex intracellular glycoprotein produced by about 90% of colorectal cancers,[2] and it can be measured quantitatively in serum. It can also be elevated in other conditions such as gastric, pancreatic, lung, breast, medullary thyroid malignancies, as well as in non-neoplastic conditions such as cirrhosis, ulcerative colitis, pancreatitis and even smoking. The serum CEA is of no value in the screening of colorectal cancer as it lacks specificity and sensitivity,[3] especially in its early stages. Despite this, primary healthcare physicians and many health-screening protocols still incorporate CEA as part of health-testing for asymptomatic individuals. This invariably results in referrals to colorectal surgeons or gastroenterologists for endoscopic evaluation for "raised CEA", which has implications for rising healthcare costs and patient anxiety.

We aimed to review all the asymptomatic patients who were referred to our department for raised CEA and who had undergone colonoscopy, and to find out if this was indeed associated with significant pathology and to what extent such patients should be investigated. We also addressed the issue of how long such patients should be followed up.

METHODS

All patients with no gastrointestinal symptoms (such as a recent change in bowel habits, perrectal bleeding, haematemesis, melaena, abdominal pain, constipation, tenesmus, and symptoms of anaemia or abdominal mass) and whose only indication for endoscopy was a raised CEA level, were entered into the study group. All the patients initially underwent evaluation with a colonoscopy. There was no standardised protocol, and often subsequent investigations were left to the attending physician. Other tests included in this initial workup were oesophagogastroscopy (OGD), abdominal imaging with either computed tomography (CT) or ultrasonography,

Table I. Results of the initial investigations.

Investigation (total no. of patients)	Pathology identified	No. of patients
Oesophagogastroscopy (173)	Stomach cancer	2
	Benign ulcers	9
	Gastric polyps	2
	Gastritis	40
Colonoscopy (217)	Colorectal cancers	11
	Stage I	2
	Stage IIa	2
	Stage IIIc	2
	Stage IV	5
	Benign polyps	31
	Size < 1 cm	25
	≥ 1 cm	6
	Colitis	2
Chest radiograph/CT (134)	Pulmonary fibrosis	6
	Primary lung cancer	5
	Lung metastases	2
Ultrasonography/CT hepatobiliary system (100)	Primary periampullary carcinoma	1
	Liver metastasis	6 (5 colonic primary)
	Ovarian teratoma	1
	Benign renal cyst	9
Mammogram (20)	None	0
Total	Primary cancers	20
	Metastatic cancers	8

and chest imaging with either chest radiography or CT of the thorax. All the investigations pertaining to the raised CEA level were retrospectively reviewed and any pathology was noted. The initial level of the CEA that led to the referral was noted, and all the subsequent CEA levels were also recorded. For statistical analysis, the proportions were compared using chi-square test or Fisher's exact test. Continuous variables were presented as median (range), and compared using Mann-Whitney U test where appropriate. Analysis was performed with the Statistical Package for Social Sciences version 11.5 software (SPSS Inc, Chicago, IL, USA). A p-value < 0.05 was considered statistically significant. Confidence intervals were defined at 95%.

RESULTS

There were 217 asymptomatic patients who presented for endoscopy and further evaluation due to raised CEA, from December 1998 to August 2004. There were 132 males and 85 females. The median age of the patients was 54 (range 22–83) years. The demographics by race was 193 Chinese, ten Malays, seven Indians and seven of other races. There were 117 smokers and 100 non-smokers. There was no demonstrable difference between the demographics and CEA value on analysis. The median CEA level at the point of referral was 6.5 ng/ml. The normal reference value used for our laboratory was a CEA level of 5 ng/ml. After the initial investigations, a total of 20 primary and eight metastatic cancers were detected (Table I). All 217 patients underwent colonoscopy, which revealed 11 colorectal cancers, 31 benign polyps (25 < 1 cm, six ≥ 1 cm) and two colitis. Initial gastroscopy diagnosed two stomach cancers, nine benign ulcers, two gastric polyps and 40 gastritis out of the 173 performed. 134 chest radiographs and CT of the thorax identified six cases of pulmonary fibrosis, five cases of primary lung cancer and two cases of metastasis in the lungs. 100 ultrasonographical scans of the hepatobiliary system or CT of the abdomen detected primary periampullary carcinoma in one patient and liver metastasis in six others (five from colonic primary and one from a lung primary). CT also detected one patient with an ovarian teratoma, and nine with likely benign renal cysts. There were no breast cancers detected in those who subsequently underwent mammogram as part of the workup. The analysis did not show a significant relationship between the levels of

Table II. Subsequent primary cancers detected on follow-up.

Pathology identified	No. of cases
Stomach	2
Lung	6
Liver	1
Ovarian	1
Prostate	1
Nasopharyngeal	3
Periampullary	1
Medullary thymoma	1
Total primary cancers	16

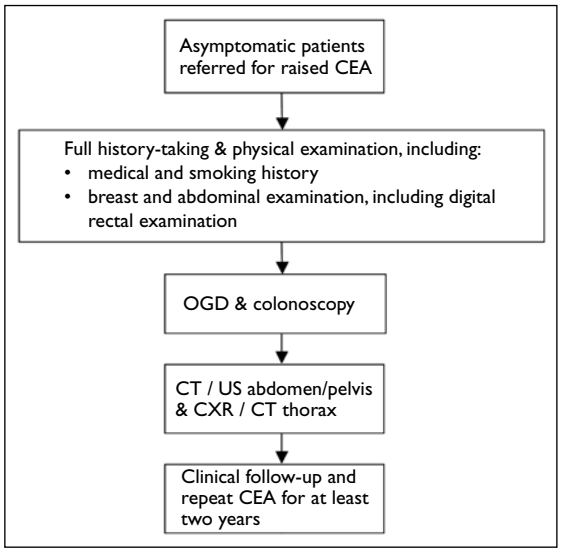

Fig. 1 Proposed algorithm for evaluating asymptomatic, average-risk patients with raised carcinoembryonic antigen.

CEA: carcinoembryonic antigen; OGD: oesophagogastroscopy; CXR: chest radiography

initial raised CEA and the detection of a malignancy.

In the subsequent median follow-up period of 13 (range 6–97) months, an additional 16 (7.4%) new primary cancers were detected from the remaining 197 patients who were not diagnosed with cancer in the initial work-up. These were diagnosed at median intervals of nine (range 1–29) months after the initial presentation and investigations, when the patients subsequently developed some symptoms and signs, which prompted further relevant investigations. Once again, a significant relationship between the level of initial or subsequent CEA and that of the secondary development and detection of a subsequent malignancy, could not be demonstrated. The breakdown of primary cancers detected were as follows: two stomach, six lung, one liver, one ovarian, one prostate, three nasopharyngeal, one periampullary and one medullary thymoma (Table II).

DISCUSSION

CEA is sensitive but not specific for colorectal cancer.[4] A raised CEA may be benign, but it has been associated with potential life-threatening malignant conditions, such as cancer of the lungs, pancreas and stomach. CEA and CA19-9 have been extensively studied for diagnosis and prognosis of pancreatic carcinoma, and most recently, for assessing expected curability and resectability.[5,6] CEA has been noted to be raised in lung neoplasms and chronic pulmonary conditions such as empyematous tuberculosis.[7] In gastric carcinoma, CEA may also contain prognostic information.[8] In colorectal cancer, CEA and CA19-9 are the most commonly-used tumour-associated antigens in the management of patients.[9] The role of CEA in colon cancer resectability and patient survival remains somewhat controversial. It has been shown to be useful in the preoperative evaluation of patients with colorectal metastasis of the liver, in assessing the prognosis either alone,[10] or in combination with other tumour markers.[11-13] Some have evaluated the role of CEA in predicting relative survival,[14] and as an independent prognostic factor in non-metastatic colorectal cancer after curative surgery.[15] However, the most commonly-accepted use of CEA would be as a sensitive predictor of colorectal cancer recurrence postoperatively.[16,17] In the follow-up of patients, a raised CEA in the absence of symptoms should prompt the clinician to investigate further with either endoscopy or by radiological means.

In our retrospective analysis, 11 colorectal cancers were detected on initial colonoscopy. Interestingly, we also detected seven non-colorectal tumours in the initial work-up of the 217 asymptomatic patients. On follow-up of these 217 patients, an additional 16 of them were found to have subsequent primary malignancies, after they developed symptoms or signs which prompted further investigations, which were not performed as part of the initial panel of tests, after a colonoscopy was done. Our primary cancer detection rate of these asymptomatic patients with raised CEA was 16.59% (36/217), which is higher than the cancer rate in the general population of approximately 240 per 100,000 (0.24%) per year. As such, the initial work-up of an asymptomatic patient with an unremarkable clinical examination should include endoscopy (i.e. colonoscopy and OGD), chest imaging and even a CT of the abdomen and pelvis, if the prior-mentioned tests are negative. While nasopharyngeal carcinoma and medullary thymoma are not associated with a raised CEA, we have nevertheless identified four patients who developed these conditions on follow-up; hence an initial increase in CEA should perhaps lead to greater vigilance as well as earlier pick-up of these subsequent cancers. Furthermore, after the initial tests, asymptomatic patients should be followed up clinically for at least two years to monitor the development of any signs or symptoms, as we suspect CEA may sometimes be elevated months after a tumour becomes evident.

Due to the retrospective nature of this study, not all the patients underwent a uniform set of investigations, such as endoscopies, imaging studies and tests for other tumour markers. As such, we hope to move on to a more standardised protocol for investigating these patients, in the form of a prospective trial. As a result of this study, a more standardised approach for investigating asymptomatic patients with raised CEA has been adopted by our department. Our approach is outlined in Fig. 1. We believe that such an approach will minimise the chances

of missed lesions. During follow-up, any further increase in CEA or specific symptoms should prompt further investigations.

In conclusion, asymptomatic average-risk patients who present with raised CEA levels should be investigated endoscopically and radiologically, for commonly-associated cancers. Although CEA is neither a specific nor accurate test for screening, patients who invariably present with a high CEA test result should be initially investigated and thereafter followed-up for at least two years, as up to a further 7.4% of them present with a subsequent malignancy. The strength of this association still remains to be evaluated with a prospective trial, which will hopefully be carried out after this pilot study.

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