Original Research Article

CEA versus Other Diagnostic Modalities for Detection of Early Recurrent Disease after Curative Resection of Colorectal Cancer

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ABSTRACT

A high serum CEA is associated with a number of malignancies, including colorectal, breast, gastric and pancreatic cancers. Many studies have shown that increased preoperative serum CEA levels are associated with an increased risk of recurrence and a poor prognosis and the prognostic effect of the serum CEA level is independent of the tumor node-metastasis stage.

Aim of the study: To evaluate the detection rate of early recurrent disease by serial CEA measurements versus other diagnostic modalities in patients after curative resection of colorectal cancer, as part of postoperative surveillance.

Material and methods: In this study, we prospectively evaluated colorectal cancer patients who were diagnosed and operated between January 1st 2012 and December 31st 2014 in the Surgical Department of Oncology and Surgery in UHC "Mother Teresa", Tirana. These patients underwent specified follow-up protocol that included: physical examination, including checking for tumor recurrence at wound sites; carcinoembryonic antigen (CEA) testing every 3 months for the first year and then every 6 months; chest radiography every 6 months for 2 years; and colon evaluation (colonoscopy), annually for the first year and then every 3 years if the colon was free of neoplasm. Recurrence was defined as either radiologic or pathologic evidence of tumor in the follow-up period. We compared the detection rate of early recurrent disease by serial CEA measurements versus other diagnostic modalities in patients after curative resection of colorectal cancer.

Results: In the evaluation of CEA detection rate versus other diagnostic modalities, we noticed a difference for a better detection rate in comparison with CT scans (33.3% vs. 23.8%; P=.747), colonoscopy (33.3% v.s. 14.2%; P=.308), Chest X-ray (33.3% vs. 9.5%; P=.159) and physical findings (33.3% v.s. 9.5%; P=.159). These differences were not statistically significant.

Conclusions: Intensive monitoring of colorectal cancer recurrence for both patient with early stages and patients with advanced stages with measurement of CEA appears to be cost-effective and superior to other diagnostic modalities.

Key words: CEA, recurrence, colorectal cancer.

INTRODUCTION

Carcinoembryonic antigen (CEA) is an acknowledged member of immunoglobulin super family, with a role as an intracellular adhesion molecule. A high serum CEA is associated with a number of malignancies, including colorectal, breast, gastric and pancreatic cancers. Many studies have shown that increased preoperative serum CEA levels are associated with an increased risk of recurrence and a poor prognosis and the prognostic effect of the

serum CEA level is independent of the tumor node-metastasis stage (Park et al., 2006; Huh et al., 2010; Yakabe et al., 2010). A multiplicity of studies carried out over the last 30 years have addressed the prognostic impact of CEA levels at initial presentation in patients with CRC. [1,2] Although these different studies varied with respect to the specific CEA assay used, cut-off point for CEA, number of patients included, follow-up period and whether or not adjuvant chemotherapy was used, almost all concluded that elevated preoperative CEA levels were associated with adverse outcome. Indeed, several of these studies showed that CEA was an independent prognostic factor and, importantly, predicted outcome in patients with stage II disease. [3-9]

Aim of the study

To evaluate the detection rate of early recurrent disease by serial CEA measurements versus other diagnostic modalities in patients after curative resection of colorectal cancer, as part of postoperative surveillance.

MATERIALS AND METHODS

In this study, we prospectively evaluated colorectal cancer patients who were diagnosed and operated between January 1st 2012 and December 31st 2014 in the Surgical Department of Oncology and Surgery in UHC "Mother Teresa", Tirana. According to the inclusion criteria, 109 patients with diagnosis of colorectal cancer after surgical treatment for this disease were recruited to the study. The excluding criteria consisted of patients with other benign conditions that influence in the CA 19-9 and/or CEA values (4 cases), patients who underwent surgery for recurrent disease (2 cases), patients with TNM stage IV disease (13 cases) and patients who were not present according to the timely protocol used (3 cases). The median age was 64 years (varying from 44 to 83 years) and 53% were female. After applying the inclusion and exclusion criteria, the study population consisted of 87 cases.

These patients underwent specified follow-up protocol that included: physical examination, including checking for tumor recurrence at wound sites; carcinoembryonic antigen (CEA) testing every 3 months for the first year and then every 6 months; chest radiography every 6 months for 2 years; and colon evaluation (colonoscopy), annually for the first year and then every 3 years if the colon was free of neoplasm. Computed tomography (CT) scans of the abdomen were at the discretion of the treating physician for symptoms, physical findings, or increased CEA values. Recurrence was defined as either radiologic or pathologic evidence of tumor in the follow-up period. We compared the detection rate of early recurrent disease by serial CEA measurements versus other diagnostic modalities in patients after curative resection of colorectal cancer.

Patient data was obtained through the medical registry and review of medical records by a single investigator. The variables evaluated included age, gender, and TNM stage.

According to the values of CEA, CEA value < 5 ng/mL was recognized as negative and these patients constituted CEA Group 1. The patients with a CEA value >5 ng/ mL were considered as CEA Group 2.

TNM stages and histological grades were noted according to histological reports. Patients with a TNM Stage I and IIA classified as Group A (early stage group), TNM stage IIB and III patients constituted Group B (advanced stage group).

Statistical analysis

The chi-square test has been used for evaluating the association between two categorical variables. The null hypothesis asserts the independence of the variables taken into consideration. Univariate and multivariate statistical methodologies were used to determine significant prognostic factors for overall survival.

RESULTS

Eighty-seven colon cancer patients were included in the trial. There were 53

patients with early-stage (stage I and IIA) and 34 patients with late-stage (stage IIB and III) colon cancer (13 patients were stage IV at primary surgery and are excluded from all subsequent analyses). Recurrence was noted in a total of 21 patients (24.1%) of which 9 had early-stage colon cancer, and 12 had late-stage disease (Table 1).

Table 1: The early recurrence rate according to the stage of the disease

TNM Stage	Cases n (%)	Early Recurrence n (%)
Stage I and IIA	53/87 (60.9%)	9/87 (10.3%)
Stage IIb and III	34/87 (39.1%)	12/87 (13.8%)
Total	**87 (100%)**	**21/87 (24.1%)**

Table 2: The methods of detection of first recurrence in early- versus late-stage colon cancer

Method used	Recurrence detection rate	Early stage (n=9)	Advanced stage (n=12)	*P value*
CEA	7/21 (33.3%)	2/9 (22.2%)	5/12 (41.6%)	*0.668*
CT scans	5/21 (23.8%)	2/9 (22.2%)	3/12 (25.0%)	*NS*
Colonoscopy	3/21 (14.2)	1/9 (11.1%)	2/12 (16.6%)	*NS*
Chest X-ray	2/21 (9.5%)	1/9 (11.1%)	1/12 (8.3%)	*NS*
Physical findings	2/21 (9.5%)	1/9 (11.1%)	1/12 (8.3%)	*NS*

In the evaluation of CEA detection rate versus other diagnostic modalities, we noticed a difference for a better detection rate in comparison with CT scans (33.3% vs. 23.8%; P=.747), colonoscopy (33.3% vs. 14.2%; P=.308), Chest X-ray (33.3% vs. 9.5%; P=.159) and physical findings (33.3% vs. 9.5%; P=.159). These differences were not statistically significant.

Figure 1: Detection of first recurrence in early- versus late-stage

We also found CEA to be more effective in detection of recurrences for

The methods of detection of first recurrence in early-and late-stage colon cancer were carcinoembryonic antigen (CEA) testing, chest radiography every, colon evaluation (colonoscopy), physical findings, computed tomography (CT) scans of the abdomen and "other" (Table 2). The difference between the detection rate in early stage versus late stage colon cancer patients was not significant for all the methods used, even for CEA testing (P=0.668).

advanced stage disease as compared with other methods used: CT scans (41.6% vs. 25.0%; P=.637), colonoscopy (41.6% vs. 16.6%; P=.411), Chest X-ray (41.6% vs. 8.3%; P=.196) and physical findings (41.6% vs. 8.3%; P=.196).

DISCUSSION

In comparison with other diagnostic modalities available, measurement of CEA series seems to be more sensitive in the early detection of the disease recurrence. [10-13] Thus, in an extensive study prospectively compared colectomy under laparoscopic assistance with open colectomy in CRC patients, measurements of CEA were superior to other diagnostic modalities for both patients with early stages (Stage I and stage IIA) and patients with advanced stages (stage IIB and stage III) disease. For the 537 patients in the early stages, 29.1% of the CEA unveiled the first recurrence, versus 23.6% by CT scanner, with 12.7% and 7.3% colonoscopy with radiography. For the 254 patients in the advanced stages of the disease, 37.4% of the CEA unveiled the first recurrence, 26.4% CT scan, chest X-ray and colonoscopy 12.1% and 8.8% respectively. [13]
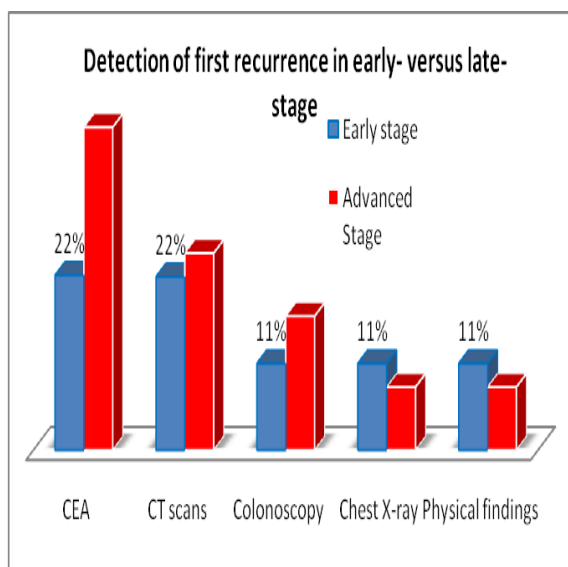
In our study we also found CEA to be more effective in detection of recurrences for advanced stage disease as compared with other methods used: CT scans (41.6% vs. 25.0%; P=.637), colonoscopy (41.6% vs. 16.6%; P=.411), Chest X-ray (41.6% vs. 8.3%; P=.196) and physical findings (41.6% vs. 8.3%; P=.196).

The difference between modalities in monitoring the disease recurrence was notable for but without statistical significance. Intensive monitoring after surgery also curative appears to be cost-effective. [14,15]

Current guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) [16] recommend at a minimum that colon cancer patients resected for cure should have CEA levels drawn every 4 months for 2 years and a colonoscopy performed at 1 year after surgery. Maximum recommendations from American Society of Clinical Oncology (ASCO), [17] and National Comprehensive Cancer Network (NCCN) [18] advise that CEA levels should be drawn every 3 months for 2 years and then twice yearly until 5 years after surgery.

In our study, CEA elevation was the single most common test identifying recurrence, and CEA was equally effective in detecting recurrence in early- and late-stage disease. One third of the patients who went on to curative secondary surgery in the COST trial were diagnosed with colonoscopy within the first 2 years with the same benefits for early- and late-stage disease patients.

In regard to the role of CT of the chest and abdomen, this type of imaging was not advised as part of the ASCRS guidelines [16] but was advised in both the ASCO [17] and NCCN [18] guidelines. Based on our data, the emphasis on lung imaging is appropriate, but the role of CT of the abdomen is less certain. It is noteworthy that with this approach 23.6% of the recurrences occurred in the lungs. Given that patients with isolated lung metastases often experience excellent 5-year survival rates

(27% to 41%), [19-21] it is recommended that patients undergo some manner of chest imaging as part of their postoperative surveillance approach. Whether annual CT of the chest is superior to a twice yearly CXR cannot be resolved at this juncture.

CONCLUSION

Intensive monitoring of colorectal cancer recurrence for both patients with early stages and patients with advanced stages with measurement of CEA appears to be cost-effective and superior to other diagnostic modalities.

REFERENCES

1. Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem 2001; 47: 624-30.
2. Goldstein MJ, Mitchell EP. Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. Cancer Invest 2005; 23:338-51.
3. Thirunavukarasu P, Sukumar S, Sathaiah M, et al. C-stage in colon cancer: implications of carcinoembryonic antigen biomarker in staging, prognosis, and management. J Natl Cancer Inst 2011;103:689-97.
4. Huh JW, Oh BR, Kim HR, et al. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. J Surg Oncol 2010;101:396-400.
5. Sun LC, Chu KS, Cheng SC, et al. Preoperative serum carcinoembryonic antigen, albumin and age are supplementary to UICC staging systems in predicting survival for colorectal cancer patients undergoing surgical treatment. BMC Cancer2009;9:288.
6. Park IJ, Choi G-S, Lim KH, et al. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. Ann Surg Oncol 2009;16:3087-93.
7. Peng Y, Wang L, Gu J. Elevated preoperative carcinoembryonic antigen (CEA) and Ki67 is predictor of

decreased survival in IIA stage colon cancer. World J Surg 2013;37:208-13.

8. Park YJ, Park KJ, Park JG, et al. Prognostic factors in 2230 Korean colorectal cancer patients: analysis of consecutively operated cases. World J Surg 1999;23:721-6.

9. Harrison LE, Guillem JG, Paty P, et al. Preoperative carcinoembryonic antigen predicts outcomes in node-negative colon cancer patients: a multivariate analysis of 572 patients. J Am Coll Surg 1997;185:55-9

10. Zugarbaker PH, Gianola FJ, Dwyer A, et al. A simplified plan for follow-up of patients with colon and rectal cancer supported by prospective studies of laboratory and radiologic test results. Surgery 1987;102:7987.

11. Rocklin MS, Senagore AJ, Talbott TM. Role of carcinoembryonic antigen and liver function tests in the detection of recurrent colorectal carcinoma. Dis Colon Rectum 1991;34:794-7.

12. Nicolini A, Ferrari P, Duffy MJ, et al. Intensive risk-adjusted follow-up with the CEA, TPA, CA19.9, and CA72.4 tumor marker panel and abdominal ultrasonography to diagnose operable colorectal cancer recurrences: effect on survival. Arch Surg 2010; 145:1177-83.

13. Tsikitis VL, Malireddy K, Green EA, et al. Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. J Clin Oncol 2009;27:3671-6.

14. Renehan AG, O'Dwyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. Br Med J 2004;328:81.

15. Graham RA, Wang S, Catalano PJ, et al. Postsurgical surveillance of colon cancer: preliminary cost analysis of physician examination, carcinoembryonic antigen testing, chest X-ray, and colonoscopy. Ann Surg 1998;228:59-63.

16. Anthony T, Simmang C, Hyman N, et al. Practice parameters for the surveillance and follow-up of patients with colon and rectal cancer. Dis Colon Rectum. 2004; 47:807-817.

17. Desch CE, Benson AB, III, and Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2005; 23:8512-8519.

18. NCCN colon cancer clinical practice guidelines in oncology. J Natl Compr Cancer Network. 2008; 1:1-MS18.

19. Tepper JE, O'Connell M, Hollis D, et al. Analysis of surgical salvage after failure of primary therapy in rectal cancer: Results from Intergroup Study 0114. J Clin Oncol. 2003; 21:3623-3628.

20. Regnard JF, Grunenwald D, Spaggiari L, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. Ann Thorac Surg. 998; 66:214-218.

21. Rena O, Casadio C, Viano F, et al. Pulmonary resection for metastases from colorectal cancer: Factors influencing prognosis: Twenty-year experience. Eur J Cardiothorac Surg. 2002; 21:906-912.

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