Evaluation of Carcino-embryonic antigen (CEA) and diagnostic significance in adult patients suffering from Colorectal Carcinoma (CRC) and GIT malignancies.

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Abstract:
Carcinoembryonic antigen (CEA) is a classic tumor marker for CRC, and has been used to monitor CRC recurrence and as a prognostic factor for CRC patients. The CEA molecule is an onco-development human tumor marker and bears the cluster differentiation designation of CD66e. It has a molecular weight of 180 kDa. Due to considerable clinical merit of CEA for diagnosis, prognosis and treatment, a study was carried out to assess its levels in patients suspected of or diagnosed with GIT cancers, with special reference to colorectal carcinoma (CRC). A total of 106 patients, 71 (66.98%) males and 35 (33.01%) females, were included in the study with age range of 46 to 79 years. Out of 71 males, 33 (46.47%) have malignant conditions and exhibited elevated levels of CEA whereas 38 have non-malignant complications with normal or non-significant CEA concentrations. The malignant conditions in males (n = 33) are sub-grouped and were determined to be pancreatic (n = 2, 6.06%), gastric (n = 10, 30.30%), colorectal (n = 18, 54.54%) and hepatic (n = 3, 9.09%) cancers. Furthermore, in female group of 35 patients, 15 (42.85%) were diagnosed with malignant condition of pancreatic (n = 1; 6.66%), gastric (n = 5; 33.33%), colorectal (n = 7; 20.00%) and hepatic (n = 2; 13.33%) cancers and exhibited elevated levels of CEA. In present study all malignant conditions, either metastasizing or not, showed significantly elevated levels of CEA. In male-malignant cancer patients’ groups, average CEA values were 102.20 40 ng/ml, 298.40 21 ng/ml, 451.65 16 ng/ml and 176.10 5 ng/ml for pancreatic, gastric, colorectal and hepatic cancers, respectively. Similarly in females elevated levels of CEA were noted in pancreatic (99 ng/ml), gastric (169.25 22 ng/ml) CRC (441.15 16 ng/ml) and hepatic (128.54 20 ng/ml). At present, serial CEA-monitoring is considered the best non-invasive technique for detecting CRC and its recurrence. It is also substantiated that intensive follow-up CEA assays facilitate the identification of treatable recurrence at an early stage.

Key Words: Carcino-embryonic antigen (CEA, Colorectal carcinoma (CRC), gastric carcinoma, Tumor marker.

Introduction:
Worldwide, colorectal cancer (CRC) is the third most common cancer diagnosed, and is associated with high rates of incidence and mortality for both men and women [1,2]. Furthermore, regardless of extensive progress in the treatment of advanced cases of CRC, the clinical outcome of this disease still remains poor [1,3]. In addition another study documented that colorectal cancer (CRC) is the second most common and the second most fatal malignancy, surveyed in
Poland, both in women (following breast cancer) and in men (following lung cancer) [4]. In Poland only in the year 2004 CRC was diagnosed in 7,049 men and 6,132 women and was the cause of death in 4,961 men and 4,377 women [4,5].

Carcinoembryonic antigen (CEA) is a classic tumor marker for CRC, and has been used to monitor CRC recurrence and as a prognostic factor for CRC patients [1]. Currently, the serum CEA test is recommended by the American Society of Clinical Oncology [6] and the European Group on Tumor Markers [7] as a prognostic biomarker for recurrent CRC following curative resection [1]. It is thoroughly documented that the CEA molecule is an onco-development human tumor marker [8-13]. It bears the cluster differentiation designation of CD66e, a subtype of CD66 group of CEA family. It has a molecular weight of 180 kDa [9,11]. In a series of studies in early 1960s, a tumor component in colon cancer tissue was found that was not present in the corresponding normal tissues [12]. In subsequent years [12], same antigen was also noted in all GIT tumors derived from endoderm. Later this antigen is designated as Carcino-embryonic antigen (CEA). After nearly 40 years since the discovery of CEA [9, 12, 13-17], until now, this tumor marker became one of the significant entities to diagnose and monitor solid tumor and the response to therapy [15-19] in GIT cancers, especially CRC [20]. Due to an immense importance of CEA in present day diagnostic and health services, a study was carried out to assess its levels in patients suspected of or diagnosed with GIT cancers, with special reference to colorectal carcinoma (CRC).

Methods and Research Protocols:
Selection Criteria
The study covered the period of Dec 2003 to Dec 2009 and includes 106 patients (Males = 71, Females = 35) in the age range of 46-79 years. A brief history of Patients was taken with clinical symptoms and signs and initial diagnosis. Patients that were admitted in wards or visiting OPDs with diagnosis or suspicions of GIT cancers and/or CRC and additional clinical conditions such as gastritis, colitis etc, were selected and classified according to gender. Their sub-groups of malignant and non-malignant status was evaluated and classified according to clinical conditions. When confirmed, their cancer status was evaluated and classified according to clinical conditions. Sample Collection: Blood (5 ml) was collected in clot activated tubes; serum was separated and stored at -10°C until analyzed.

Analysis and Calculation:
All CEA analysis was performed in duplicates by Automated ECL technology with two - point calibration and controls with preci-normal and preci-path levels on Elecsys 2010 (Roche Diagnostics, Basel) automated immunoassay-analyzer. For accuracy purpose, CEA values greater than two folds of 10.0 ng/ml were considered significant. Normal range is between 2.5-5.0 ng/ml. All data were statistically compared with student’s t tests and where required Pearson’s correlation analysis using SPSS ver 11.0 program with P < 0.01. Data of patients’ are also presented in the form of percentage occurrence for clarity.

Results:
The results are summarized in Table I-II and Figures 1-2. Briefly, 106 patients, 71 (66.98%) males and 35 (33.01%) females, were included in the study with age range of 46 to 79 years. Out of 71 males, 33 (46.47%) have malignant conditions and exhibited elevated levels of CEA (189 ng/ml to 532 ng/ml; mean = 334.45 ± 68 ng/ml), whereas 38 have non-malignant complications with normal or non-significant (> 12 ng/ml but < 25 ng/ml) CEA concentrations. Malignant conditions in 33 patients were determined to be pancreatic (n = 2, 6.06%), gastric (n = 10, 30.30%), colorectal (n = 18, 54.54%) and hepatic (n = 3, 9.09%) cancers. In female group of 35 patients, 15 (42.85%) were diagnosed with malignant condition of pancreatic (n = 1; 6.66%), gastric (n = 5; 33.33%), colorectal (n = 7; 46.66%) and hepatic (n = 2; 13.33%) cancers and exhibited elevated levels of CEA (133
ng/ml to 441 ng/ml, mean 311.20 45.40 ng/ml). Non-malignant conditions were found to be hepatitis, cirrhosis, pancreatitis (acute and obstructive) and gastritis. In present study all malignant conditions, either metastasizing or not, showed significantly elevated levels of CEA. In male-malignant cancer patients' groups, average CEA values were 102.20 40 ng/ml, 298.40 21 ng/ml, 451.65 16 ng/ml and 176.10 5 ng/ml for pancreatic, gastric, colorectal and hepatic cancers, respectively. Similarly in females elevated levels of CEA were noted in pancreatic (99 ng/ml), gastric (169.25 22 ng/ml) CRC (441.15 16 ng/ml) and hepatic (128.54 20 ng/ml).

Discussions:
Ever since the discovery of CEA by Gold et al [21] and its characterization in mid 1960s, it has become the one of the most broadly known tumor markers for gastrointestinal tract diseases, especially significant for CRC diagnosis [1]. To this date, several studies have been extensively performed to investigate the role of prognostic factors for survival in patients with CRC [22]. Of many parameters, preoperative carcino-embryonic antigen (CEA) level had previously been demonstrated to be a predictive factor of recurrence [23-25]. In present study we have reported assessment of CEA in male and female patients suspected off or diagnosed with GIT cancers, especially CRC. It was observed that, CEA is a significant biochemical marker to evaluate and determine GIT cancers, with considerable specificity in CRC and gastric cancers. Substantial elevated values of CEA were noted in all groups of male and female patients diagnosed with malignant diseases of pancreatic, gastric, CRC and hepatic carcinoma. Commonly considered cut-off point for CEA is 2.5-5.0 ng/ml for distinguishing normal from abnormal level of serum or plasma. Survey conducted with vast population of healthy persons showed that 85% to 87% had serum CEA level less than 2.5 ng/ml, 95% to 98% less than 5.0 ng/ml and none had level greater than 10.0 ng/ml [26-30]. Moreover, CEA concentration is often found raised in smokers than in non-smokers. Elaborated efforts have also been made in 1970s and 1980s to review the clinical usefulness of CEA through a larger forum of international scientists and researchers [26-28]. It is concluded that the diagnostic utility of CEA is established in adenocarcinoma of colon, where 80% or more of patients showed increased level of circulating CEA. However, suggestions were made that CEA assay alone should not be used as the sole diagnostic test. As stated earlier, CEA level, greater than the cut-off value of 5.00 ng/ml but less than 10.00 ng/ml, may also detected in non-malignant conditions, such as liver diseases.

This has also been reported that there is a rise in both frequency of positive CEA assay and the plasma CEA level, with increasing tumor burden. Example is the incidence of positive CEA assay in patients with Dukes stages A (20%), to Dukes stages D (90%) colon cancer. Significant CEA elevation ranging from 18% to 79%, was demonstrated in patients with colon cancer of Dukes stage A, B1, B2, C1 and C2 [31-34]. In a recent study, preoperative levels of serum CEA were found to be significantly associated with tumor size and T category, but not with N category or tumor differentiation [1]. Moreover, preoperative CEA levels also found proportional to the stage of disease, with providence of prognostic determinant of survival. These results are in agreement with the studies reported earlier [1, 35-37], and also established that elevated levels of serum CEA correspond to an independent prognostic factor for 5-year DFS, especially for diagnosed cases of stage II A and III B CRC [1]. It is argued that serum CEA assay alone, have not been a useful marker in the screening and diagnosis of colon cancer. However, it plays an important role in the clinical management of patients with colorectal adenocarcinoma [38, 39]. In this respect, the application of monoclonal antibody (mAB) technique targeting CEA have shown promising results due to high sensitivity for diagnosing colon adenocarcinoma. In colon cancer, CEA modulates intercellular adhesion, functions as a promoter of cellular aggregation, regulates the innate immune system, and mediates signal transduction [1, 40-42]. Accordingly, it is
hypothesized that CEA plays an important role in tumor invasion and metastasis. In this study, the 5-year DFS rate of stage II CRC patients with elevated levels of serum CEA were compared with stage III CRC patients with normal levels of serum CEA, and no significant difference was found [1]. This researched outcome is coherent with an earlier report and suggests that a diagnosis of CRC be associated with elevated levels of serum CEA may be an indicator for tumor restaging even after surgery. Furthermore, it has been reported that genetic vaccines marking CEA may be a feasible strategy for the treatment of CRC [1, 43, 44]. For instance, it was observed that stage II CRC patients with elevated levels of CEA may be entrant for adjuvant chemotherapy following curative resection surgery [1, 45].

Prognostic utility of CEA in patients with CRC and some other cancers have been thoroughly investigated. Pre-operative serum levels are found to be elevated in 40% to 70% patients with CRC [46-48]. Pre-operative CEA levels are also found to correlate inversely with tumor grade and directly with pathological grade. Therefore, it is documented that CEA is raised in 95% of patients with well-differentiated tumors, whereas only 30% in poorly differentiated adenocarcinoma. Several studies have demonstrated that a significant inverse relationship exist between pre-operative plasma CEA levels and patients’ survival, suggesting poor prognosis [49, 50]. CEA is also an important prognostic marker of breast cancer. In most case studies, the pre-operative CEA levels have been found to correlate with poor prognosis. It is suggested that, the group at a higher risk of relapse could be determined based on preoperative CEA concentration and clinical staging of the disease [4]. Other authors demonstrated that prognosis in patients with elevated preoperative CEA concentration was poorer and that CRC relapse was more common in these patients [4, 51]. Similarly, in other studies higher preoperative CEA concentration was observed in relapsed patients (5.3 vs 3.5 ng/ml) and the chance of second resection in these patients was lower [4, 52, 53]. In the investigated group there were 68.75% patients with advanced CRC and in these patients relapse was significantly more common [4]. Moreover, pre and post-operative or treatment levels of CEA may also serve as a good prognostic marker in breast, stomach and lung cancers.

In conclusion, currently, treatment monitoring and evaluation of possible relapse are the most significant area of CEA assay. A post-operative raise in CEA level in patients undergone a treatment regime strongly suggest recurrence of tumor. At present, serial CEA-monitoring is considered the best non-invasive technique for detecting recurrent CRC. Numerous studies substantiated that intensive follow-up CEA assays facilitate the identification of treatable recurrence at an early stage. The studies are in progress in our department to correlate pre and post-operative values of CEA with diagnosis and prognosis of CRC and GIT cancers in general.

References:


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