The predictivity of Carcino-Embryonic Antigen (CEA) level in detecting liver metastasis in colorectal cancer

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ABSTRACT

Objective: To investigate the relationship between the level of Carcino-Embryonic Antigen (CEA) and the presence of colorectal liver metastasis in patients with colorectal cancer.

Methods: This retrospective study was conducted at colorectal unit at King Hussein Medical Center (KHMC). All patients who were diagnosed with colorectal cancer (CRC) at our colorectal surgery unit from January 2015 to may 2017 were included in the study. Data collected and analyzed included demographics, smoking habits, location of tumor, the presence of distant metastasis and the level of CEA. The primary outcome was to compare presence of distant metastasis between the two groups. Secondary outcome included the CEA level elevation with regard to age, gender and smoking. Sixty five patients with abnormal CEA level (study group) were compared to 82 patients with normal CEA levels (control group).

Results: One hundred and forty seven patients were included in our study. There were 78 males (53.1%) and 69 females (46.9%) with a mean age of 59.2 years (range 27-86 years). Seventy three patients were smokers (49.7%). Liver metastases were present in 40 patients (27.2%). Seventy nine patients who had normal CEA level had no liver metastasis (96.3%), while three patients had normal CEA level and presence of metastasis (3.7%), negative predictive value of 96.34 %. On the other hand, 28 patients with elevated CEA level had no liver metastasis (43%) and 37 patients with elevated CEA level had liver metastasis (56.9%), positive predictive value of 56.92%. P value (0.016)

Conclusion: Normal CEA levels significantly predict the absence of liver metastasis in CRC patients. Elevated CEA levels were not affected by age and gender. Strong association between CEA levels along with metastatic trend.

Key words: Carcinoembryonic antigen, Colorectal cancer, Liver metastases, Tumor markers.

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Introduction

The incidence of colorectal cancer (CRC) is increasing worldwide. [(1)] It was the leading cause of cancer related deaths in Jordan and accounted for 2.2% of the total deaths in 2012. [(2)] The best treatment option for CRC remains radical surgery. [(3)] High rates of CRC metastasis and recurrence have produced a poor overall survival and prognosis. [(4,5)] For this reason, an identification of certain prognostic parameters become necessary to start improving survival rates in CRC patients. Tumor markers are required for assessment of cancer risk, screening, diagnosis, prognosis, prediction, and monitoring after treatment. [(6)] In CRC patients, the most widely used tumor marker is carcino-embryonic antigen (CEA) which

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was discovered in 1965 by Gold and Freedman who described its presence in adult colonic cancerous tissue and embryonic digestive tissue; for which reason they called it CEA.[7] CEA Levels are predominantly applied as tumor markers to monitor CRC treatment, to stage or localize cancer and to identify spread or recurrences after surgical resection.[8] CEA levels may also be elevated in gastric carcinoma, pancreatic carcinoma, lung carcinoma, breast carcinoma, and medullary thyroid carcinoma, in addition to some non-neoplastic conditions like liver cirrhosis, ulcerative colitis, pancreatitis, Crohn's disease, hypothyroidism, and COPD.[9,10] Up till now the reliability of CEA in diagnosing and screening for early detection of CRC is not established and it is a matter of debate in the scientific community. This study is trying to assess the role of CEA levels in prediction of CRC metastasis and its behaviour in relation to certain variables like age, gender and smoking.

Methods:

This is a retrospective study which was conducted at a quaternary care center over a period of 29 months (January 2015 to May 2017). Carcino-embryonic antigen (CEA) levels were collected at day of admission for 147 adult patients who were diagnosed radiologically and histopathologically to have colorectal cancer at our colorectal surgery unit. 65 patients with abnormal CEA level (study group) were compared to 82 patients who were having normal CEA levels (control group). Data including demographics, smoking habit, presence of distant metastasis were collected. Distant metastasis was defined as presence of colorectal lung or liver metastasis proved by radiological investigation (US, CT scan). CEA levels were classified into normal levels (control group) if equal or less than 5 nanograms per milliliter (ng/ml) in non-smokers but equal or less than10 ng/ml in smokers, and abnormal levels (study group) if more than 5 ng/ml in non-smokers but more than 10 ng/ml in smokers. Primary outcome was to compare presence of distant metastasis in study group and control group. Secondary outcomes include attitudes of CEA levels in respect to age, gender and smoking habits. Approval by our institution ethical committee was obtained for study conduction and publication. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 21 software. Descriptive statistics are displayed as means, frequencies and percentages. Chi-square test and Spearman correlation coefficient were used when appropriate. 95% confidence intervals (95%CI) were used to identify predictive values, sensitivity and specificity. A *p* value less than 0.05 is considered statistically significant.

Results:

One-hundred and forty seven patients with colorectal cancers at our institute were included in this study. There were 78 (53.1%) males and 69 females (46.9%) with a M:F ratio about 1.1:1. The mean age ±SD for the whole cohort was 59.18±13.38 years (range 27-86) with more than 72.8% of the patients more than 50 years old. Smoking habits were found in 49.7% of patients.CEA levels were Abnormal in 58 patients (39.5%). Metastatic trends were positive in 40 patients (27.2%). The primary endpoint in the study design was to assess the relation between CEA levels and distant metastasis. As shown in Table I, 57% of the study group showed metastasis in comparison to 3.7% of control group, while absence of metastasis was found in 43%, 96.3% of both groups respectively. The calculated sensitivity of CEA level was 92.5% with specificity of 73.8%. The positive predictive value was 56.92%, 95% CI (48.71% to 64.77%) while negative predictive value was 96.34 %, 95% CI (89.81% to 98.74%); for which reasons we conclude the significant association between abnormal CEA levels and presence of distant metastasis with a *p*-value of 0.016. Logistic regression was used to analyze predictors of having an abnormal CEA levels in the study group. (Table II & III) Gender status failed to show significance as a risk factor for high levels of CEA; with 43.5% of females compared to 35.9% of males in the study group had abnormal CEA levels and insignificant p-value of 0.401. The percentage of patients in the study group aged between 20-50 years was 35% in comparison to 41% were more than 50 years

which exhibit insignificant relationship between age and CEA levels with *p*-value of 0.616. On the other hand we found a strong correlation of abnormal CEA levels with smoking habits in which 45% of smoker have high levels of CEA which accounts for approximately 57% of the study group with a p-value of 0.025

Table I: CEA levels with metastatic attitude.

	Metastasis			**CEA Level**
	Normal		Total	P- Value
Total				
	NO	High		
	79 (96.3%)	28 (43%)	107	.0160
Yes				
	3 (3.7%)	37 (57%)	40	

Table II: Predictors of Abnormal CEA levels

Criteria	**Number of patients**	**Abnormal CEA level**	**P- value**
Gender:			
Male	78	28 (35.9%)	.4010
Female	69	30 (43.5%)	
Age:			
20-50 years	40	14 (35%)	.6160
>50 years	107	44 (41%)	
Smoking Habits:			
Yes	73	33 (45%)	.0250
No	74	25 (34%)	

Table III: Regression analysis of variables.

		Parameter Estimates							
VAR00001[a]		**B**	**Std. Error**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% Confidence Interval for Exp(B)**	
								Lower Bound	Upper Bound
Normal	Intercept	-2.446	1.284	3.629	1	.057			
	Gender	-.388	.462	.707	1	.401	.678	.274	1.677
	Age	-.009	.017	.252	1	.616	.991	.959	1.025
	Smoking	1.073	.478	5.044	1	.025	2.924	1.146	7.459
	[Mets=.00]	3.722	.667	31.187	1	.000	41.361	11.200	152.741
	[Mets=1.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: high.
b. This parameter is set to zero because it is redundant.

Discussion:

CRC incidence has been expanded all over the world and become one of the leading causes of cancer deaths; and to cope with such an expansion multiple strategies should be adopted by health centers including implementation of cancer screening programs and proper utilization of tumor markers measurements along with the clinical scenarios of CRC patients to detect cancers at early stages, to indicate further investigations and to be used in prognostic prediction as well as expecting whether a specific therapy for a certain stage will work or not.[6] Studies reporting the prognostic values of tumor markers are still poor.[11] The most widely used tumor marker in CRC is CEA; such biomarker along with thorough clinical analysis could be used as an alternative for CRC early diagnosis and bring in hopefully new targets in management of CRC patients.[12] Nowadays the comparative success of surgery in resecting distant metastasis (liver or lung) arising from primary colorectal cancers makes it necessary to determine CEA levels as baseline and serial one to help in early detection of cancer spread into liver or lungs.[8] The primary outcome in this study was to compare metastatic status between both study and control groups which was significantly different (57% vs 3.7%,

p=0.016), and this result goes along with many other studies on the subject,[13-19] but contrasts a study published by Yoshikawa *et al* who reported that high CEA level is independent predictive factor for cancer recurrence or metastasis.[20] It is generally believed that CEA level measurements are not recommended in screening for CRC in general population but testing of CEA levels can improve the diagnostic sensitivity for early detection of CRC.[21] In our study the average ± SD of CEA levels was 3.35 ± 2.20 in control group vs 146.5 ± 471.9 in study group. The calculated sensitivity and specificity of CEA was found to be 92.50% (95% CI 79.61% to 98.43%), 73.83 % (95% CI 64.45% to 81.85%) respectively. The positive predictive value of CEA was 56.92% vs 96.34 % for the negative predictive value of CEA with accuracy of 78.91% (95% CI 71.42% to 85.20%). These results were in concordance with Duffy and Tomasevic *et al*.[8,21] Although not used in screening and diagnosis of CRC; presence of high levels of CEA pre- and post-operatively strongly predicts the metastatic behavior of CRC and may be included in staging procedures pre-operatively as well as restaging post-operatively.[13,18,19,21-25]

It is well known that many cancerous conditions are associated with elevated levels of CEA like cancers of esophagus, stomach, liver and pancreas, where benign conditions like inflammation, pregnancy, gynecological disease, smoking and hepatitis have been related to variable changes in CEA levels.[16] The secondary endpoints in our study were to analyze the behavior of CEA levels in respect to age, gender and smoking.We found no significant relations between age and gender of CRC patients and CEA level with a *p*-value of 0.616 and 0.401 respectively. These results come in agreement with previous studies on the same subject.[16,21,22,25] However when we analyzed the correlation of smoking habits with CEA levels; there was a significant relationship between them with a *p*-value of 0.025. Earlier studies in literature support our result when Duffy in his mini review of literature in 2001 found that smoking almost double the concentration of CEA levels in CRC patients.[8] In the same context Zhenqiang *et al* found in both univariate and multivariate analysis that CEA levels significantly affected by smoking in CRC patients.[16] Finally, it is worth mentioning what Catherin *et al.* stated in their publication in 2008 that although a *p*-value reflects a statistical significance, it is not the only influential criterion for clinical utility, and that a single study doesn't set up a scientific fact; actually we need to secondarily validate the results of a study in which the same assay and cut-off points should be applied in the validation study. [6]

Limitations of the study:

The limitations we had in our study are the non-randomization of study and control groups and retrospective nature of study, the cut-off points are not standard in the whole literature; we apply the most widely used ones, and the insufficient data about post-operative histopathology reports; so relation of CEA levels with staging not achieved.

Conclusion:

Normal CEA levels significantly predict the absence of liver metastasis in CRC patients. Elevated CEA levels were not affected by age and gender. Strong association between CEA levels along with metastatic trend. Secondary validation of the study in a set including same assay and cut-off points along with correlating CEA levels with tumour stage would be imperative.

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