RESEARCH ARTICLE

Prognostic significance of pre- and post-operative serum carcinoembryonic antigen levels in patients presented with rectal carcinoma; an experience from Shaukat Khanum Memorial Cancer Hospital and Research Center Lahore

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Abstract

Objective: To explore the importance of serum carcinoembryonic antigen level as a tumour marker in rectal carcinoma.

Method: The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan, and comprised data of patients with rectal carcinoma from January 1996 to December 2015. Serum carcinoembryonic antigen levels were analysed using immulite@2000 system analyser. On the basis of serum carcinoembryonic antigen levels, data of patients was divided into four groups. Group A had normal serum levels both before and after surgical resection; Group B had normal levels pre-surgery but post-surgery levels were raised; Group C had raised levels pre-surgery that went down to normal post-surgery; and Group D had raised levels both before and after surgery. SPSS 23 was used for data analysis.

Results: Of the 401 patients, 267(66.6%) were males, and 204(50.9%) were aged <50 years. Group A had 267(66.6%) patients, Group B 26(6.5%), Group C 79(`9.7) and Group D had 29(7.2%) patients. Stage III disease was the most common 343(85.5%) and it was true across the groups. Overall recurrence was in 141(35.2%) patients. Group D had the highest recurrence rate 26(89.7%), while Group C had the lowest 18(22.8%).

Conclusion: Fluctuating levels of carcinoembryonic antigen affected post-operative outcome.

Keywords: Carcinoembryonic antigen, Rectal carcinoma, Colonoscopy. (JPMA 69: 1442; 2019). **doi:10.5455/JPMA.292193**

Introduction

Rectal carcinoma is one of the common health problems and has serious associated morbidities and mortality issues.[1] The degree of penetration of the primary lesion (T stage) and nodal status (N stage) provide a gross overview of tumour stage and possible disease prognosis and relapse of tumour after primary surgery. However, different patients with the same tumour-node-metastasis (TNM) staging behave differently in terms of disease prognosis and relapse.[2] So identification of risk factors for tumour prognosis and relapse is a challenging domain. For this reason it is advisable to check pre-operative parameters other than TNM staging to identify the factors that are responsible for tumour recurrence after curative primary resection of the rectal cancer.[3,4]

One of the most commonly used tumour markers for colorectal carcinoma is serum carcinoembryonic antigen (CEA). Serum CEA has high expression in adenocarcinoma, it is an easily available, and is a cost-effective test. That is why it is the most commonly used tumour marker for surveillance and assessment of disease relapse in rectal cancer patients.[5] Raised pre-operative serum CEA levels have been associated with advanced tumour stage, poor tumour response to neo-adjuvant chemo-radiotherapy and increased risk of recurrence after curative primary resection.[6] It has also been shown in previous studies that raised post-operative serum CEA level has prognostic significance for rectal cancer in terms of disease relapse.[7]

Simultaneous evaluation of pre- and post-operative serum CEA levels to have any prognostic significance in rectal cancer is seldom assessed. The current study was planned to explore the importance of serum CEA levels as a tumour marker in predicting clinical outcome, tumour prognosis, tumour relapse, disease-free survival (DFS) and overall survival (OS) for patients with rectal carcinoma.

Materials and Methods

The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital (SKMC), Lahore, Pakistan, and comprised data of patients with rectal carcinoma who had presented to the Surgical Oncology Department from January 2006 to December 2015. Data of all patients with rectal cancer who had undergone curative surgical resection and in whom serum CEA samplings was performed using IMMULITE@2000 systems

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Analyzer in pre- and post-operative period was included. Data related to patients with more than one primary cancer and those with missing serum CEA levels was excluded. Staging work-up included full colonoscopy, contrast-enhanced computed tomography (CT) scan of thorax and abdomen, and magnetic resonance imaging (MRI) of pelvis. This had been done in all cases mainly to exclude patients having advanced cancer with distant metastasis.

After approval was taken from the institutional review board, clinical data of all patients, including age, gender, clinical presentation, clinical and pathological TNM classification, pre- and post-operative CEA levels at follow-up, histopathological findings, tumour recurrence, DFS and OS, was collected from patient's records. Serum CEA levels had been monitored for a period of one year from the date of primary tumour resection surgery. Depending upon the serum CEA levels in pre- and post-operative period, data of all patients in the study was categorised into four groups. Group A patients had normal serum CEA levels both before and after surgical resection of primary tumour. Group B comprised patients with normal serum CEA levels before surgery while after surgery, serum CEA levels were raised. Group C comprised patients with raised serum CEA levels before surgery which came down to normal after resection of primary tumour. Group D comprised patients with raised serum CEA levels in both before and after the surgery. Serum CEA level of 4.6 was taken as the cut-off upper limit, with levels >4.6 considered to be raised.

Data analysis was done using SPSS 23. Mean +/- standard deviation (SD) was used for continuous variables, while frequencies and percentages were used for categorical variables, like recurrence / pre-operative CEA levels / OS etc. Categorical variables were compared using Chi square test or Fisher's exact test when necessary. To estimate survival, Kaplan Meier method was applied, while Log rank test was used for the analysis of survival difference. Statistical significance was defined as two-tailed p=0.05.

Results

Of the 612 patients who presented with rectal carcinoma, 434(71%) had undergone curative resection. Of them, 33(7.6%) were excluded due to missing data, while the remaining 401(92.6%) comprised the final sample. Of the total, 267(66.6%) were males, and 204(50.9%) were aged <50 years. Group A had 267(66.6%) patients, Group B 26(6.5%), Group C 79(`9.7) and Group D had 29(7.2%) patients (p>0.05). Gender had no impact in group comparison (p=0.92). In clinical staging (cTNM), 343(85.5%) patients had stage III disease. On pathological staging (pTNM), 78(19.5%) patients had stage I disease, 84(20.9%) had stage II, 157(39.2%) had stage III and 3(0.7%) had stage IV disease, while 79(19.7%) had no residual tumour showing complete pathological response. Resection margin was positive in 27(6.7%) (Table-1).

Table-1: Descriptive statistics (Baseline characteristics - n= 401).

Variables	Characteristics	Frequency N (%)
Age in years	up to 50	204 (50.9%)
	Above 50	197 (49.1%)
Gender	Male	267 (66.6%)
	Female	134 (33.4%)
cTNM	Stage I	7 (1.7%)
	Stage II	44 (11.0%)
	Stage III	343 (85.5%)
	Stage IV	7 (1.7%)
pTNM	Complete response	79 (19.7%)
	Stage I	78 (19.5%)
	Stage II	84 (20.9%)
	Stage III	157 (39.2%)
	Stage IV	3 (0.7%)
Carcinoembryonic antigen level	Group A: Both Normal	267 (66.6%)
	Group B: Pre-Op Normal & Post-Op Raised	26 (6.5%)
	Group C: Pre-Op Raised & Post-Op Normal	79 (19.7%)
	Group D: Both Raised	29 (7.2%)
Recurrence	No	260 (64.8%)
	Yes	141 (35.2%)
Over all Recurrence free survival in months	Mean ± SD	35.63 ± 21.05
Margin clearance	No	27 (6.7%)
	Yes	374 (93.3%)
Outcome status	Alive	352 (87.8%)
	Dead	35 (8.7%)
	Loss to follow-up	14 (3.5%)

cTNM: Clinical tumour-node-metastasis
pTNM: Pathological tumour-node-metastasis
SD: Standard deviation.

On the basis of TNM staging, most patients were stage III in all four groups followed by stage II (Table-2). Circumferential resection margin was positive in 6(23.1%) patients of group B and 4 (13.8%) of group D (p=0.004). Overall recurrence was found in 141(35.2%) patients, while 206(64.8%) were without any recurrence on long-

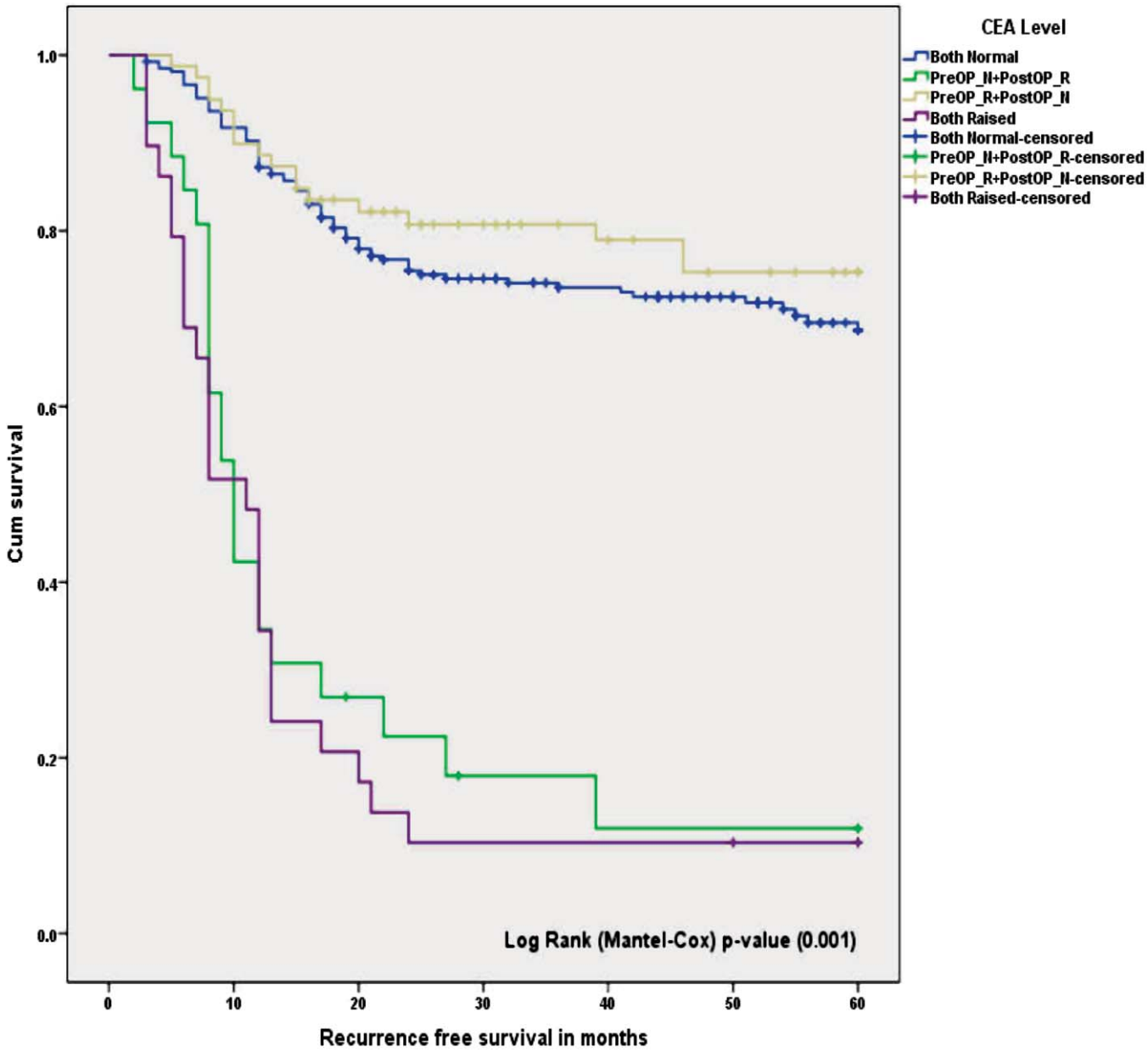

Figure-1: Kaplan Meir curve for recurrence/ disease-free survival in months.

term follow-up with a mean DFS of 35.63±21.05 months. Group D had the highest recurrence rate 26(89.7%), while Group C had the lowest 18(22.8%). Groups A and C had a higher 5-year DFS compared to groups B and D (Figure-1). Similarly, OS in groups A and C was much better compared to groups B and D (Figure-2).

Discussion

CEA is a widely used tumour marker for colorectal cancers and it has been evaluated through several studies for its association with disease extent, prognosis, disease recurrence and DFS as well as OS status of the patients. Tumour extension and outcome after surgical resection mostly depends on pre-operative serum CEA levels, while disease recurrence and patient survival status mainly depend on post-operative serum CEA levels.[8,9] In some patients, high pre-operative serum CEA levels failed to return to normal after successful surgical resection of the primary tumour with no residual disease behind. Association of pre- and post-operative serum CEA levels and their effects on tumour relapse after curative primary surgical resection were seldom studied.[10] Therefore the

Table-2: Characteristics of patients with Carcinoembryonic antigen (CEA) levels.

Variables	Group A: Both Normal 267 (66.6%)	Group B: Pre-Op Normal & Post-Op Raised 26 (6.5%)	Group C: Pre-Op Raised & Post-Op Normal 79 (19.7%)	Group D: Both Raised 29 (7.2%)	p-value
Age in years					
up to 50	144 (53.9%)	14 (53.8%)	34 (43.0%)	12 (41.4%)	0.25
Above 50	123 (46.1%)	12 (46.2%)	45 (57.0%)	17 (58.6%)	
Gender					
Male	177 (66.3%)	16 (61.5%)	54 (68.4%)	20 (69.0%)	0.92
Female	90 (33.7%)	10 (38.5%)	25 (31.6%)	9 (31.0%)	
cTNM					
Stage I	5 (1.9%)	1 (3.8%)	0 (0.0%)	1 (3.4%)	0.07
Stage II	31 (11.6%)	4 (15.4%)	5 (6.3%)	4 (13.8%)	
Stage III	229 (85.8%)	21 (80.8%)	71 (89.9%)	22 (75.9%)	
Stage IV	2 (0.7%)	0 (0.0%)	3 (3.8%)	2 (6.9%)	
pTNM					
Complete response	64 (24.0%)	2 (7.7%)	11 (13.9%)	2 (6.9%)	0.04
Stage I	49 (18.4%)	6 (23.1%)	18 (22.8%)	5 (17.2%)	
Stage II	54 (20.2%)	3 (11.5%)	21 (26.6%)	6 (20.7%)	
Stage III	99 (37.1%)	14 (53.8%)	29 (36.7%)	15 (51.7%)	
Stage IV	1 (0.4%)	1 (3.8%)	0 (0.0%)	1 (3.4%)	
Margin clearance					
No	13 (4.9%)	6 (23.1%)	4 (5.1%)	4 (13.8%)	0.004
Yes	254 (95.1%)	20 (76.9%)	75 (94.9%)	25 (86.2%)	
Recurrence					
No	192 (71.9%)	4 (15.4%)	61 (77.2%)	3 (10.3%)	0.001
Yes	75 (28.1%)	22 (84.6%)	18 (22.8%)	26 (89.7%)	
Outcome status					
Alive	240 (89.9%)	21 (80.8%)	70 (88.6%)	21 (72.4%)	0.01
Dead	21 (7.9%)	2 (7.7%)	8 (10.1%)	4 (13.8%)	
Loss to follow up	6 (2.2%)	3 (11.5%)	1 (1.3%)	4 (13.8%)	

cTNM: Clinical tumour-node-metastasis

pTNM: Pathological tumour-node-metastasis (mentioned here just for the ease of readers).

present study was conducted to explore the importance of serum CEA level as a tumour marker in rectal cancer patients for prognosis in terms of disease recurrence, DFS and OS.

There are reports indicating that post-operative serum CEA levels can be influenced by clinical and pathological features like gender, tumour depth and lymph node metastases.[11] European group guidelines on tumour markers also showed that serum CEA levels possessed independent prognostic value for disease relapse and patient survival status.[12] The current study presented a correlation between abnormal pre- and post-operative serum CEA levels with American Joint Committee on Cancer (AJCC) stages. In line with literature, our study also highlighted that advanced stage significantly correlated with higher pre- and post-operative serum CEA levels. For this reason we, together with literature, suggest that serum CEA levels should be added to the current staging system.[13]

A high concentration of post-operative serum CEA levels during follow-up predicts an adverse outcome in terms of disease relapse, DFS and OS. Rectal cancer-related mortality can be significantly reduced with early detection of disease relapse as it will lead to early treatment and, thus, increase the chances of survival.[14]

CEA has shown promise as an indicator of residual disease before recurrence becomes clinically apparent, and patients with recurrence might be cured if the residual disease is identified and treated effectively earlier. Studies have reported that in 18-75% cases prior to any clinically observable recurrence, post-operative serum CEA levels rise, and, hence, give a good clue to keeping such patients on close follow-ups and treat such patients effectively at an early stage.[15] This rise has been reported as early as 4 months prior to recurrence[15] and it is possible to detect recurrence at an earlier stage. In the present study, 89.65% patients who had raised pre- and post-operative serum CEA levels and 84.61% patients with normal pre-operative but raised post-operative serum CEA levels

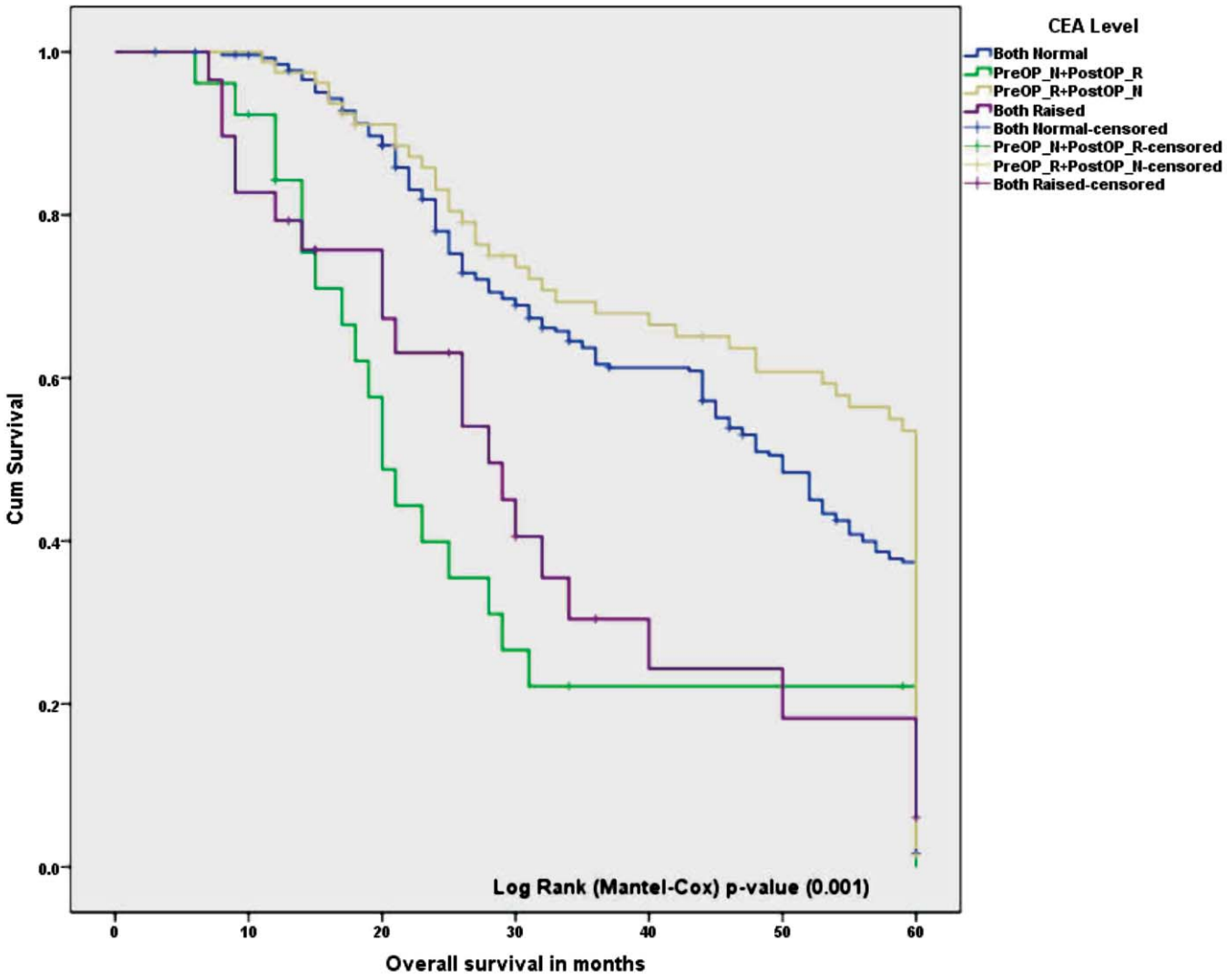

Figure-2: Kaplan Meir curve for overall survival in months.

developed recurrence on follow-up. This showed that a raised serum CEA level in post-operative course is an indication for disease relapse.

Goldstein et al. stated that raised pre- and post-operative serum CEA levels are indicative of systemic disease.[16] A study suggested that if pre- and post-operative serum CEA levels remain higher, they may be an indicator of increased risk.[17] These results are similar to those of the current study.

The current study showed improved OS in patients who had normal pre- and post-operative serum CEA levels or those in whom pre-operative levels were raised, but post-operatively they returned to normal values. It concluded that patients with raised post-operative CEA levels exhibited poor outcome.

In our opinion, rectal cancer patients whose post-operative serum CEA levels continue to remain high should be followed up closely and extensively and should be considered for adjuvant chemotherapy.

The current study has its limitations as it is a retrospective study with a small number of patients for analysis at a single institution. We recommend a prospective multi-centre study with a large number of patients for analysis to validate the results.

Conclusion

Isolated pre-operative serum CEA levels, if elevated, had no association with recurrence and disease prognosis but if pre- and post-operative serum CEA levels were higher or postoperative serum CEA levels increased in a patient with normal pre-operative serum CEA levels, it had a poor

prognosis and worse outcome.

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Conflict of Interest: None.

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