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Original Article

Serum CA 19.9 as a Tumour Marker in Colorectal Cancer Staging- An Experimental Study

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Abstract

This cross-sectional, descriptive observational study was carried out for a period of 24 months from January 2014 to December 2015 in the Department of Pathology and Department of Surgery, Rajshahi Medical College, Rajshahi for estimation of serum 19-9 level in total fifty four patients. Histopathological Staging was correlated with the preoperative values of serum CA 19-9 level. Data were collected by face to face interview, clinical examination and findings of laboratory investigations. Preoperative serum CA 19-9 levels were estimated by Enzyme Linked Immunosorbent Assay (ELISA) Method. The study revealed that the colorectal carcinoma was highest in the 5th and 6th decade and rectal area (46.3%) and male predominance was observed with male to female ratio being 3:2. A higher incidence of abnormal CA 19-9 level was found in Dukes' D (100%) and Dukes' C (84%) diseases than in Dukes' B (76%) and Dukes' A (75%) stages. The sensitivity of CA 19-9 in correctly detecting advanced stage CRC carcinoma from those who had early stage of the disease is (36/44) × 100 = 81.8% and its specificity in correctly excluding those who did not have advanced disease is (2/10) × 100 = 20%. The overall diagnostic accuracy is calculated to be (36 + 2)/54 = 70.37%. Regarding diagnostic values for colorectal carcinoma elevated level of serum CA 19-9 can be considered as an important diagnostic tool for differentiating advanced stage of colorectal carcinoma from its early stage

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Introduction

Colorectal Carcinoma is one of the leading causes of Cancer-related death.[1,2] Colon Cancer is equally affects both men and women.[3] It is the third most common Cancer in men. In Bangladesh it is the third most common Cancer in case of male (10.1%) and fourth (10%) most common Cancer in case of female.[4] Tumour Markers are used clinically as an adjunct to diagnosis, staging, and monitoring of the disease.[5] Tumour Markers are proteins released from dying Tumor cells or produced by neoplastic cells.[6] CA 19-9 is cancer antigens that are late markers of colorectal cancer, with significantly elevated serum concentrations in case of colon cancer with already developed metastasis.[5] In 99.6% of healthy adults, serum CA 19-9 levels are lower than 37 u /ml. CA 19-9 is not specific for early detection of colon cancer, meaning they cannot be used in the diagnosis of carcinoma in situ.[7] CA 19-9 is also used in preoperative staging and postoperative follow-up of patients, especially patients who are treated

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with chemotherapy. The appearance of elevated levels of CA 19-9 markers in the serum is in most cases a sign of recurrence or metastatic lesions in near environment of the tumor as well as remote ones.[7] The CA 19.9 assay level decreases after therapy and increases in cases of relapse, residual disease and metastasis.[8] The Carbohydrate Antigen 19-9 (CA 19-9) has been described as potentially useful in the diagnosis of colorectal carcinoma.[9,10] Multiple studies have shown that while elevations in serum CA 19-9 appear to be useful in the diagnosis monitoring of colonic carcinoma.[11] and in monitoring of colonic Carcinoma. Elevations of CA 19-9 level correlate with the degree of tumour differentiation as well as the extent of tumour mass.[12,13] A decrease in the CA 19.9 assay level can indicate a positive response to therapy and therefore good prognosis.[14,7] A constant increase of the CA 19.9 assay value often reflects evolution of the Tumor and a poor response to therapy. Its concentration is correlated with the Tumor size.[15] Thus, tumors of smaller size have normal serum concentrations of CA 19.9. Only Tumors greater than 3 cm are accompanied with high concentration of CA 19.9 antigen.[16] CA 19-9 increases parallel with tumour spread, with the highest values recorded in patients with metastasis.[17] Increase of its concentration for a period of few months after the surgery is speaking in favour of recurrence.[18] CA 19-9 levels is related to tumor grade with the highest levels found in the more anaplastic tumors. The aim of detecting the circulating levels of CA 19-9 level is to provide a critical and update review on the value of CA 19-9 as apoptotic markers of colorectal carcinoma and its correlation with tumour size, histologic type and stage.

Materials and Methods

This Cross sectional, descriptive observational study was carried out for a period of 24 months from January 2014 to December 2015 in the department of Pathology and department of Surgery, Rajshahi Medical College, Rajshahi for estimation of serum 19-9 level in total fifty four patient. All the patients with clinically diagnosed and later on histopathologically confirmed as colorectal carcinoma were included in this study considering excluding criteria like Clinically suspected patients but not confirmed as colorectal carcinoma histopathologically and patients with upper GIT infection, Gall bladder infection, Hepatic infection Inflammatory bowel diseases, pancreatitis. A pre-tested questionnaire was used to collect data from the cases and serum CA 19.9 level will be determined by ELISA method. All biopsy specimens will be collected in 10% formalin. Then tissue would be transported to the department of pathology, Rajshahi medical college for histopathological examination. Careful gross examination was done with particular emphasis to the size, shape and colour of biopsy. The specimen was subjected to routine examination. The haematoxylin and eosin stained slides were critically examined to evaluate histological features. Histological staging was done with commonly used histological grading given by Koss LG & Melamed MR, 2006. Accuracy of a screening test against an established diagnosis like Sensitivity, Specificity, Positive predictive value of the test, Negative predictive value of the test, Diagnostic accuracy were calculated. The data was be analyzed with the help of SPSS software programme.

Results

The study revealed that the colorectal carcinoma was highest in the 5th and 6th decade and rectal area (46.3%) and male predominance was observed with male to female ratio being 3:2. In terms of Duke's staging, 14.8% were in Stage A, 38.9% in stage B, 35.2% in stage C and 11.1% in stage D. As per TNM staging 42.6% of the tumours invaded through muscularis propria into subserosa or non-peritonialised pericolic or perirectal tissue (T3), 38.9% invaded directly into other organs or structures and/or perforates visceral peritoneum (T4), 16.7% invaded mucularis propria (T2) and only 1.9% invaded submucosa (T1). In about 59.3% of the tumours, no regional lymph node (LN) metastases took place (N0), in 29.6% cases

metastases took place to 1-3 pericolic or perirectal LNs (N1), in 5.6% cases metastases occurred in 4 or LNs (N2). In only 3.7% cases metastases was seen along the vascular trunk of the organ (N3). Metastases to distant organ occurred in only 4(7.4%) cases (M1) (Table I). Level of CA 19-9 > 37 U/ml was considered as elevated. Accordingly 81.5% of patients had raised CA 19-9 (Table II). The accuracy or validity of serum CA 19-9 in differentiating advanced stage of colorectal carcinoma from its early stage is shown in table III. According to the formulae for computation of the components of accuracy, the sensitivity of CA 19-9 in correctly detecting advanced stage colorectal carcinoma from those who had early stage of the disease is (36/44) × 100 = 81.8% and its specificity in correctly excluding those who did not have advanced disease is (2/10) × 100 = 20%. Likewise the positive and negative predictive values of the serum CA 19-9 are (36/44) × 100 = 81.8% and (2/10) × 100 = 20% respectively. The percentages of false positive and false negatives are (8/44) ×100 = 18.2% and (8/10) × 100 = 80% respectively. The overall diagnostic accuracy is calculated to be (36 + 2)/54 = 70.37% (Table III). In diagnosing of advanced staged of colorectal carcinoma the tumour marker CA 19.9 and histopathology are almost comparable (p=0.600).

Table I. Distribution of patients by tumour staging (n = 54)

Staging	Frequency	Percentage
Duke's staging		
A	8	14.8
B	21	38.9
C	19	35.2
D	6	11.1
Total	54	100%
TNM staging		
Depth of tumour invasion (T)		
T1	1	1.9
T2	9	16.7
T3	23	42.6
T4	21	38.9
Total	54	100%
Extent of nodal metastases (N)		
N0	32	59.3
N1	16	29.6
N2	3	5.6
N3	2	3.7
Total	54	100%
Status of distant metastasis (M)		
M0	48	88.88
M1	6	11.11

Table II. Distribution of patients by level of serum CA 19-9 (n = 54)

CA 19-9 (U/ml)	Frequency	Percentage
≤ 37	10	18.5
>37	44	81.5

Table III. Accuracy of CA 19-9 in diagnosing advanced stage of colorectal carcinoma (n=54)

S. CA 19-9 (U/ml)	Histopathologic Comment		Total
	Advanced (stage 3 & 4)	Early (stage 1 & 2)	
Elevated (> 37 U/ml)	36	8	**44**
Not elevated (≤ U/ml)	8	2	**10**
Total	**44**	**10**	**54**

Discussion

The present study focused on frequency of colorectal carcinoma, their anatomical distribution, Histologic grading and staging of the diseases and their correlation with Carbohydrate antigen 19-9 (CA 19-9) serum level. The CA 19-9 is a tumour associated, but not a tumour specific antigen and is synthesized by normal human pancreatic and biliary ductular cells, as well as by gastric, colonic, endometrial and salivary epithelia[19] and has been found in normal seminal fluid saliva, bile, ovarian cyst fluid, amniotic fluid, gastric and duodenal secretions, and urine.[20] This explains the elevated level of CA 19-9 in many diseases, raised against human colonic carcinoma cell line has been used as a tool for the investigation and management of patients with colorectal carcinoma.[21] The study revealed that the colorectal carcinoma was highest in the 5th and 6th decade and rectal area (46.3%) and male predominance was observed with male to female ratio being 3:2. Galante et al in 1996[22], Iversen et al in 2005[23] and Floyd et al in 1992[24] reported the peak incidence in the 6th decade and rectal area and a male predominance.

In this study a higher incidence of abnormal CA 19-9 level was found in Dukes' D (100%) and Dukes' C (84%) diseases than in Dukes' B (76%) and Dukes' A (75%) stages. Zheng et al. in 2009[25] and *Abdullah et al in 2013[26] reported* significantly increased levels of CA 19-9 in patients with advanced Dukes stage and TNM stage in colorectal cancer patients. In terms of histopathological grading 20.37% of the tumours were poorly differentiated, 44.44% moderately differentiated and 35.2% well-differentiated. Number of cases with colorectal carcinoma had CA 19.9 levels more than 100 u/ml were 3 in well differentiated, 5 in moderate differentiated and 9 in Poor differentiated. Zora et al in 2013[27] reported higher incidence of abnormal CA 19-9 level in poor differentiated colorectal carcinoma. In this study the sensitivity of CA 19-9 in correctly detecting advanced stage CRC carcinoma from those who had early stage of the disease is (36/44) × 100 = 81.8% and its specificity in correctly excluding those who did not have advanced

disease is (2/10) × 100 = 20%. The overall diagnostic accuracy is calculated to be (36 + 2)/54=70.37%. Kuusela et al. (1984)[28] found sensitivity for the CA 19-9 assay 36%. Colorectal Working Group of The American Joint Committee on Cancer (AJCC)[29] recommend Serial CA 19-9 determination to detect recurring CRC has a sensitivity of 70-80% and a specificity of 80- 90%.

Conclusion

In the present study, the CA 19-9 levels with TNM stages in colorectal cancer patients revealed that increased CA 19-9 level was an indicator of advanced stage (Dukes C and D). Positivity for CA 19-9 tumour markers was found to be an important indicator of advanced stage. Elevated CA 19-9 values related with the histologic grade. Poorly differentiated colorectal carcinoma had mean CA 19-9 values 133.48 U/ml in the study. Different results available in the literature suggest that further studies including larger populations are required.

References

1. Chan, C.C., Fan, C.W., Kuo, Y.B., Chen, Y.H., Chang, P.Y., Chen, K.T., Hung, R.P. & Chan, E.C. (2010) Multiple serological biomarkers for colorectal cancer detection. Int J Cancer, 126, 1683-1690.
2. Zhao-Hut, H., Li-Hua, L., Fan Y& Jin-Fu, W. (2007) Detection of apparent methylation in fecal DNA as a molecular screening tool for colorectal cancer and precancerous lesions. World J Gastroenterol, 14, 950-954.
3. Rosai, j. (2004) Gastrointestinal tract, surgical pathology, MOSBY, 1st Louis, USA 9th ed. Vol. 1, pp 863-862
4. Wahed, T.B.(2012) Distribution of cancer patients and patterns of cancer treatment at Dhaka medical college hospital, Bangladesh. IRJP, 3(4) 157-161
5. Zora Vukobrat-Bijedic, Azra Husic-Selimovic, Amela Sofic, Nina Bijedic, Ivana Bjelogrlic, Bisera Gogov, Amila Mehmedovic (2013) Cancer Antigens (CEA and CA 19-9) as Markers of Advanced Stage of Colorectal Carcinoma. Med Arh, 67(6), 393-396
6. Magnani, J.L., Steplewski, Z.& Kiprowsk, Z (1983) Identification of gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. Cancer Res, 43, 5489-5492.
7. Reiter, W., Steiber, P., Reuter, C. et al (2000). Multivariate analysis of the prognostic value of CEA and CA 19-9 serum levels in colorectal cancer. Anticancer Res, 20, 5195-8
8. Park, Y.A., Lee, K.Y., Kim, N.K. et al (2006). Prognostic effect of perioperative change of serum carcinoembryonic antigen level: a useful tool for detection of systemic recurrence in rectal cancer. Ann Surg Oncol, 13, 645-50.
9. Herlyn, M., Sears, H.F., Steplewski, Z & Koporwski, H. (1982) Monoclonal antibody detection of a circulating tumor- associated antigen. I. Presence of antigen in sera of patients with colorectal, Cancer Res, 48, 3834-3842.
10. Kopacova, M., Tacheci, I., Rejchrt, S.(2009) Peutz-Jeghers syndrome: diagnostic and therapeutic approach. World J Gastroenterol,15,5397-5408.
11. Kouri, M., Pyrhonen, S. & Kuusela, P. (1992) Elevated CA 19-9 as the most significant prognostic factor in advanced colorectal cancer. J Surg Oncol, 49, 78-85
12. Malesci, A., Tommasini, M.A., Bonato, C. (1987) Determination of CA 19-9 antigen in serum and pancreatic juice for differential diagnosis of pancreatic adenocarcinoma from pancreatitis. Gastroenterology, 92, 60-67.
13. Yakabe, T., Nakafusa, Y. & Sumi, K. (2010) Clinical significance of CEA and CA 19-9 in postoperative follow-up of colorectal cancer. Ann Surg Oncol, 17, 2349-56.
14. McLeod, H.L. & Murray, G.I. (1999). Tumour markers of prognosis in colorectal cancer. Br J Cancer, 79, 191-203
15. Wang, W.S., Lin, J.K., Chiou, T.J., Liu, J.H., Fan, F.S., Yen, C.C. et al. (2002) A 19-9 as the most significant prognostic indicator of meta-static colorectal cancer. Hepatogastroenterology, 49(43), 160-164.
16. Kannagi, R., Izawa, M., Koike, T., Miyazaki, K., Kimura, N. (2004) Carbohydrate-mediated cell adhesion in cancer metastasis and angiogenesis. Cancer Sci, 95(5), 377-384
17. Mario, P., Massimo, D. P., Daniela, B., Glovannil, R., Alda, G., Fabrizio, G., & Augusto, C. (1996) Serum Tumor Markers in Colorectal Cancer Staging, Grading, and Follow-Up. Journal of Surgical Oncology, 62, 239-244
18. Katoh, H., K. Yamashita, Y. & Kokuba, (2008) "Surgical resection of stage IV colorectal cancer and prognosis," World Journal of Surgery, vol. 32, no. 6, pp. 1130–1137
19. Rhodes, M. & Ching, C. (1990) Serum diagnostic tests for pancreatic cancer. Clin Gastroenterol, 4, 835-852.

20. Villano, B.C. & Zurawski, V.R. Jr. (1983) The carbohydrate antigenic determinant 19.9 (CA 19.9): a monoclonal antibody defined tumor marker. In Abisi RM, Hyun J, eds. Immunodiagnostics. New York: Alan R. Liss, pp 269-282

21. Koprowski, H., Steplewski Z., Mitchell, k., Herlyn, M. (1979) Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genet, 5, 957-971.

22. Galante, M., Dumphy, J.E., Fletcher, W.S. (1996). Cancer of colon. Ann surd, 165,732-44

23. Iversen, L.H., Pedersen, A., Riis, S., Friis, S., Laurberg (2005) Population based study of short and long term survival from colorectal cancer in Denmark, 1995-1999. British journal of surgery, 92, 873-880

24. Floyd, C.E., Corley, R.G., John, J.R. (1992). Local recurrence of carcinoma of colon and rectum. Ann J surg, 109,153-59

25. Zheng, C., Liu, H., Wengi, D. K., Honghong, W., Donghong, Y., Xiaoli, H. et al.(2009) Detection of serum gastric cancer-Associated MG7-Ag from gastric cancer patients using a Sensitive and Convenient ELISA Method. Cancer Investigation, 27, 227-233.

26. Abdullah S, Mustafa K, Gurhan B, Fatih B, Orhan A (2013) CEA and CA 19-9 are Still Valuable Markers for the Prognosis of Colorectal and Gastric Cancer Patients. Asian Pac J Cancer Prev, 14 (7), 4289-4294

27. Zora Vukobrat-Bijedic, Azra Husic-Selimovic, Amela Sofic, Nina Bijedic, Ivana Bjelogrlic, Bisera Gogov, Amila Mehmedovic (2013) Cancer Antigens (CEA and CA 19-9) as Markers of Advanced Stage of Colorectal Carcinoma. Med Arh, 67(6), 393-396

28. Kuusela, P., Jalanko, H. & Roberts, P. (1984) Comparison of CA 19.9 and carcinoembryonic antigen (CEA) levels in the serum of patients with colorectal diseases. Br J Cancer, 49, 135-139.

29. American Cancer Society Fact Sheet. Tumor Markers. Available at: http://www. cancer.org/acs/groups/cid/documents/webcontent/003189-pdf.pdf (Accessed: January 3, 2012).

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