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Effect of VEGF-1 Expression in Colorectal Cancer on Clinic Pathological Outcome and Impact of Anti VEGF in Metastatic CRC with Intact Primary Tumor

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Colorectal cancer (CRC) is third leading cause of cancer mortality. About 60% of patients had already developed metastasis at the time of diagnosis. Tumor growth and metastasis are dependent on angiogenesis. Evidence from preclinical and clinical studies indicates that vascular endothelial growth factor (VEGF) is the predominant antigenic factor in CRC. There is an unmet need for predictive markers for the antiangiogenic agent bevacizumab in metastatic colorectal cancer (mCRC). We aimed to assess whether the location of the primary tumor is associated with bevacizumab effectiveness when combined with Chemotherapy (FOLFOX) in the first-line treatment of patients with mCRC.
Patients and Methods: A group of 17 consecutive patients with mCRC from the general community treated from January 2018 to October 2019 with FOLFOX and bevacizumab as standard first-line therapy was compared with a group of 17 patients treated with FOLFOX from January 2018 to October 2019. Main outcome measures were progression-free survival (PFS). Differences in survival outcome were analyzed.

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Results: Patients treated with FOLFOX and bevacizumab with primary tumors originating in the left colon and rectum had a significantly better outcome than patients with primary tumors originating from the right colon. This difference was confirmed in multivariate analyses after adjustment for other potentially prognostic factors. For patients treated with FOLFOX, there was no association between primary tumor location and outcome, neither in unadjusted nor adjusted analyses.
Conclusions: The addition of bevacizumab to FOLFOX in first-line treatment of patients with mCRC improved progression free survival than patients treated by FOLFOX alone.

Keywords: Colorectal cancer; CRC; VEGF; mCRC.

1. INTRODUCTION

Colorectal cancer (CRC), also referred to as cancer of the colon or rectum is one of the major causes of cancer deaths worldwide (IARC, 2002). Global Cancer Statistics in 2008, stated that colorectal cancer is the second most common cancer in females and third in males and with over 1.2 million new cases and 608,700 deaths estimated to have occurred [1,2,3].

It was estimated that in 2015, there were 106,100 new cases of colon cancer (52010men 54090 women) and 40870 new cases of rectal cancer (23580 men and 17290 women) diagnosed. In 2015, 49920 Americans (25240 men and 24680 women) were predicted to die of colorectal cancer. It remains the second leading cause of cancer death in the United States [4-7]. The lifetime risk for the development of colorectal cancer in the united states is 5.5% (1/18) for men and 5.1% (1/20) for women [8,9].

VEGF-1 expression seems to provide valuable prognostic information in CRC, particularly in selecting those patients at high risk for disease progression who are likely to benefit from adjuvant therapy [8].

They are important signaling proteins involved in both vasculogenesis and angiogenesisVascular endothelial growth factor (VEGF), originally known as vascular permeability factor (VPF), is a signal protein produced by cells that stimulates the formation of blood vessels. To be specific, VEGF is a sub-family growth factors, the platelet-derived growth factor family of cystine-knot growth factors [9,10].

In this study we had investigated the VEGF expression in unresectable metastatic colorectal cancer and also the effect of anti VEGF therapy on disease outcome in metastatic colorectal cancer patient with intact primary tumour.

2. METHODS

The study was conducted on patient that attended the causality and OPD and admitted for metastatic colorectal cancer. All the admitted patients were investigated for VEGF-1 expression and according to VEGF-1 expression patients are divided into two groups seen in the department of general surgery, Associate LLR Hospitals, GSVM Medical College, and J.K. Cancer Institute, Kanpur from January 2018 to October 2019.

- Inclusion criteria were Unresectable Histological and radiological proven metastasis. Exclusion criteria were other coexisting malignancy other than colorecectal.
- Patients group having VEGF positive expression treated by chemotherapy + anti VEGF and group having negative VEGF expression treated by chemotherapy alone. Disease outcome evaluation was done by using computed tomography(CT) scan abdomen and thorax at 4 month and 8 month after end of the chemotherapy and by Response Evaluation Criteria In Solid Tumour (RECIST) 1.0 criteria.

2.1 Data Extraction

From the retrospective data, all patients who came within the study period were contacted using their respective phone numbers or that of their relatives. The objectives of the study were explained to them. They were made to know that their participation was entirely voluntary.

- Primary tumour location right colon, left colon and rectum and VEGF expression was registered.

- Progression of disease was evaluated by CT scan and showing progression according to the RECIST 1.0 criteria.

3. RESULTS

Total 34 patient were categorized in 6 age groups. The result shows that majority of patient were in 55-64 age group. The mean age of the patient was 51.

Most of the patients of well differentiated adenocarcinoma are mucinous adenocarcinoma. Out of all patient of mucinous adenocarcinoma had VEGF positive expression.

The study of FOLFOX plus bevacizumab versus FOLFOX alone as first line treatment of mCRC showed a larger benefit of bevacizumab on progression free survival (PFS).

In Table 2, Chi-square test applied, P value is 0.0014, at P<0.05, test was significant. The progression free period for patients treated by chemotherapy plus anti-VEGF is more and significant than patient treated by chemotherapy alone.

Table 1. Histopathological differentiation

VEGF Expression	Well differentiated	Moderately differentiated	Poorly differentiated
Positive	5	8	4
Negative	4	10	3

Table 2. Number of patients showing progression after full cycle of chemotherapy

Duration of follow-up	Chemotherapy alone	Chemotherapy+Anti-VEGF-1
Progression After 4 month	11 (64.7%)	2 (11.8%)
Progression After 8 month	6 (35.3%)	15 (88.2%)

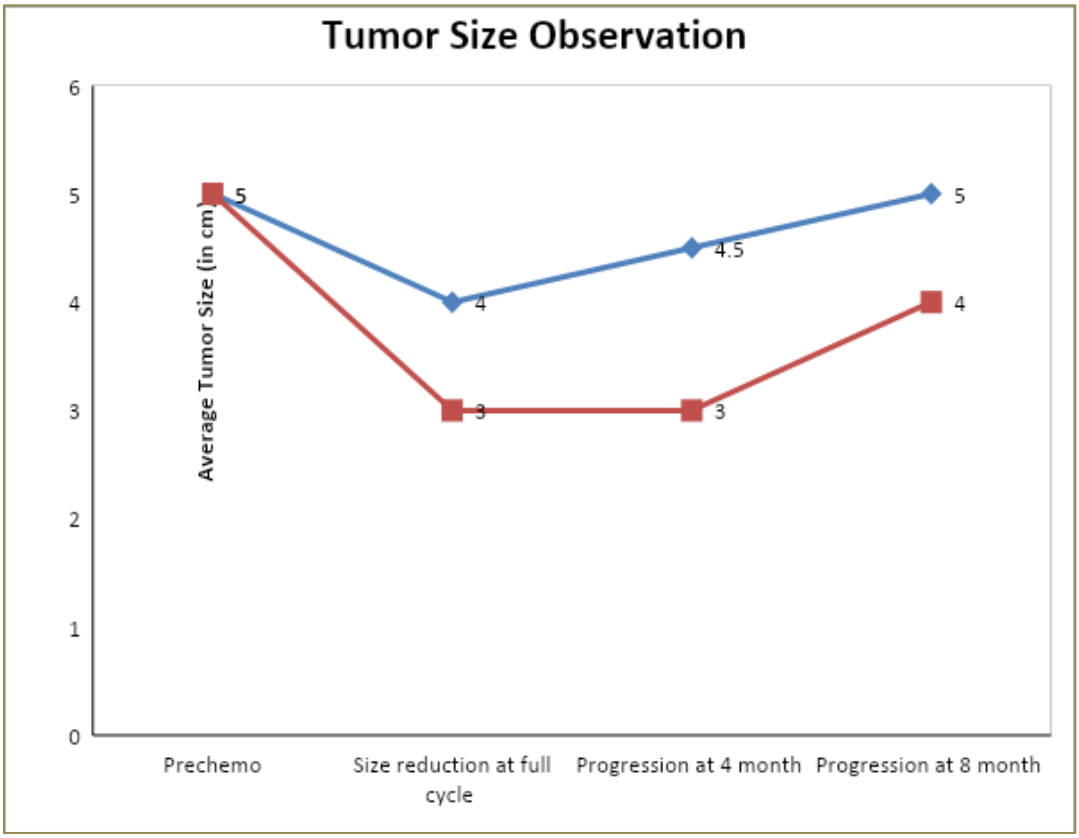

Fig. 1. Tumor size observation

In this study 64.70% patient treated by chemotherapy alone developed progression of tumour after 4 month after the end of chemotherapy and 35.30% patient after 8 month of end of chemotherapy.

In Patients who were treated by chemotherapy plus anti-VEGF, only 11.80% patient developed tumour progression after 4 month after the end of chemotherapy and 88.20% patient after 8 month of end of chemotherapy.

4. DISCUSSION

In this exploratory analysis, we have provided evidence for a possible interaction between location of the primary tumor and effectiveness of bevacizumab treatment in patients with mCRC. The data were collected from the general surgery department of LLR Hospital, GSVM Medical College, and J.K. Cancer Institute, Kanpur with the standard treatment. In our study the mean age of the patient was reported as 51. The mean age reported was similar to that reported in B Lee et al (2016) which was 51.6 of 67 years in his study of 113 patients [11]. Majority of patient in our study was males M:F ratio was 6:3 Out of 34 patients 21(61.8%) were males and 13 (38.94%) were females. Maximum number i.e. 34 patients of colorectal cancer, in 17 (50%) patient primary site of distribution of cancer was rectum site followed by left colon i.e in 15 (44.1%) patients. When divided into two categories according to localization as right colon vs. left colon and rectum, VEGF expression in the right colon was significantly less frequent than that in the left colon and rectum (44% vs. 50%, respectively) (p=0.31). Seventy percent (70%) of patients with stage IV CRC had positive VEGF expression compared to 30% who had negative expression, while 50% and 47%, respectively, (p=0.005) patients with stage II and III disease had positive VEGF expression. In our study 50% patient have VEGF positive expression. In our study patient treated by chemotherapy plus anti-VEGF in comparison to chemotherapy alone was associated with significant longer progression free survival P=0.0014. Chi-square test applied, P value is 0.0014, at P<0.05, test was significant. The progression free period for patients treated by chemotherapy plus anti-VEGF is more and significant than patient treated by chemotherapy alone. In this study 64.70% patient treated by chemotherapy alone developed progression of tumour after 4 month after the end of chemotherapy and 35.30% patient after 8 month of end of chemotherapy. In Patients who were treated by chemotherapy plus anti-VEGF, only 11.80% patient developed tumour progression after 4 month after the end of chemotherapy and 88.20% patient after 8 month of end of chemotherapy.

5. CONCLUSION

The addition of bevacizumab to FOLFOX in first-line treatment of patients with mCRC improved progression free survival than patients treated by FOLFOX alone.

CONSENT AND ETHICAL APPROVAL

Informed consent was sought from the subjects. As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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