# EARLY PREDICTABILITY FACTORS IN PROGNOSTICATION OF COLORECTAL CARCINOMAS- A STUDY

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**ABSTRACT**

**BACKGROUND**

Colorectal malignancies are one of the leading causes of cancer related morbidity and mortality in the present day. There is a substantial deficit in the reporting and analysis of the said malignancies in the Indian subcontinent. Most CRCs are sporadic, although genetic factors increase the risk considerably. Identification of Prognostication Factors at the time of diagnosis helps in predicting the tumour behaviour and helps the clinician in treatment decision making.

**MATERIALS AND METHODS**

This is a descriptive observational study, which was done for 2 years. During this study period, patients admitted in general surgery wards of IPGME and R and SSKM Hospital, Kolkata (a tertiary care centre) with colorectal carcinoma were included in the study. After initial treatment, they were followed up for 5 months. In this study, non-metastatic and diagnosed cases of colorectal carcinoma were included.

**RESULTS**

In our study, even though the elderly age was affected more, the incidence among the younger age group was alarming. Certain preoperative factors like higher stage of the disease and CEA level more than 5 IU were associated with poor outcome. Certain postoperative histopathological factors like poorly differentiated tumours, high-grade tumours, presence of residual tumour, presence of lymphovascular invasion and MSI-L status were associated with poor prognosis.

**CONCLUSION**

Assessment of certain factors, both pre-operatively and post-operatively can guide us towards prediction of the final outcome of the patient in terms of complete cure or the risk of recurrence or metastasis.

**KEY WORDS**

Prognostic Factors, Colorectal Carcinomas, Microsatellite Instability (MSI), Serum CEA, Lymphovascular Invasion.

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## BACKGROUND

Colorectal malignancies are one of the leading causes of cancer related morbidity and mortality in the present day with greater incidence in the developed world and a constantly increasing presence in a developing nation like ours. There is a substantial deficit in the reporting and analysis of the said malignancies in the Indian subcontinent. The Indian population, along with vast numbers also presents a genetic diversity and a whole new perspective in the development of the disease, its progression and response to treatment.

In India, the annual incidence rates (AIR) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th.[1,2]

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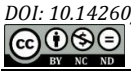

In a recently conducted study of 224 colorectal tumours by the Cancer Genome Atlas Network, the pattern of genomic alterations in colon and rectal tissues was found to be similar, regardless of the anatomic location and origin. The researchers concluded that tumours of the colon and rectum can be grouped together.[3] Most CRCs are sporadic, although genetic factors increase the risk considerably.[4]

Prognostic factors are those that help to indicate disease outcomes. Identification of these factors at the time of diagnosis helps in predicting the tumour behaviour and helps the clinician in treatment decision making. The College of American Pathologists (CAP) convened a Prognosis Factors Consensus Conference to evaluate the role of biologic, genetic, molecular and other tissue-based factors on colorectal cancers.[5]

These factors were grouped into categories based on the strength of the published evidence evaluating their prognostic value.

An attempt is made via this study to attain a prospective analysis of various colorectal malignancies in the native population with their clinico-pathological correlation, prognosis, response to the modalities of care available and as per the guidelines prescribed after various meta-analysis of literature in the developed world.

**Aims and Objectives**

1. To study the clinico-pathological profile of the patients presenting with colorectal carcinomas in IPGME and R, Kolkata and SSKM Hospital.
2. To study certain prognostication factors for colorectal carcinomas in these patients.
3. To see any distant metastasis or any recurrence at the end of 6 months of follow-up.

**MATERIALS AND METHODS**

This is a descriptive observational study, which was done for 2 years. During this study period, patients admitted in general surgery wards of IPGME and R with colorectal carcinoma were included in the study. After initial treatment, they were followed up for 5 months.

1. Study Area: IPGME and R and SSKM Hospital, Kolkata (Tertiary Care Centre).
2. Study Population: Patients admitted in general surgery wards of IPGME and R and SSKM Hospital with diagnosis of colorectal carcinoma.
3. Sample Size: 50 cases of newly diagnosed colorectal carcinoma who were admitted in the general surgical wards from June 2015 to December 2016 were chosen as the study subjects.
4. Study Design: Descriptive observational study.
5. Parameters to be Studied: Clinico-pathological profile, some prognostication factors and any disease recurrence or metastasis at the end of the follow-up period.
6. Study Tools: Pre-designed and pre-tested proforma.
7. Data Collection Procedure:
   - Questionnaire.
   - Clinical examination.
   - Review of investigations.
   - Follow-up data.
8. Data Analysis Procedure: Relevant analytical statistical methods including tables, bar diagrams, pie charts and Chi-square test for the test of significance.

**Inclusion Criteria**

Non-metastatic and diagnosed cases of colorectal carcinomas.

**Exclusion Criteria**

Previously treated patients with colorectal carcinoma, currently admitted for recurrence of the same disease were excluded.

**RESULTS**

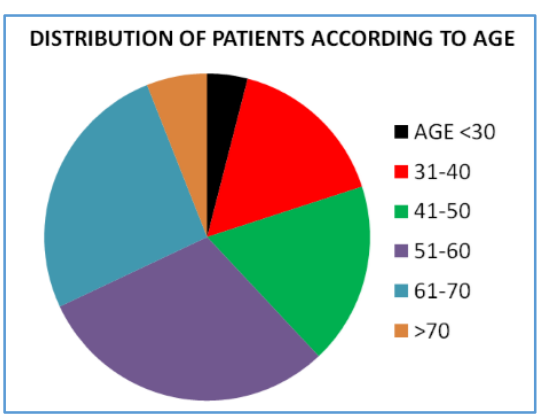


***Figure 1***

In our study, the Mean Age of the population was 51 years. The Standard Deviation was 13.59. The most common age group affected was 51 - 60 yrs. (Fig. 1).

| | Frequency | Percentage |
|---|---|---|
| Male | 22 | 44% |
| Female | 28 | 56% |
| **Total** | **50** | **100%** |

***Figure 2***

The majority of patients were female in our study (Fig. 2).

| COMPLAINTS- ABH | FREQUENCY | PERCENT |
|---|---|---|
| ABH PRESENT | 32 | 64% |
| ABH ABSENT | 18 | 36% |
| TOTAL | 50 | 100% |

***Figure 3***

Abnormal bleeding per rectum history (ABH) was present in 64% patients (Fig. 3).

| | FREQUENCY | PERCENT |
|---|---|---|
| LOW PRESENT | 29 | 58% |
| LOW ABSENT | 21 | 42% |
| TOTAL | 50 | 100% |

***Figure 4***

Loss of Weight (LOW) was seen in 58% of the patients (Fig. 4).

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| ABDOMINAL DISTENSION | 13 | 26% |
| MASS PER ABDOMEN | 3 | 6% |
| FEVER | 6 | 12% |
| NO COMPLAINTS | 28 | 56% |
| TOTAL | 50 | 100% |

***Figure 5***

Abdominal distension was a frequent symptom among the patients (Fig. 5).

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| NO PAST HISTORY OF MALIGNANCY | 47 | 94% |
| BREAST CARCINOMA | 1 | 2% |
| OVARIAN CARCINOMA | 1 | 2% |
| PROSTATE CARCINOMA | 1 | 2% |
| TOTAL | 50 | 100% |

***Figure 6***

6% of the patients had past history of any related malignancy (Fig. 6).

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| SMOKING | 13 | 26% |
| SMOKING + ALCOHOL | 7 | 14% |
| NO HISTORY OF ADDICTION | 30 | 60% |
| TOTAL | 50 | 100% |

***Figure 7***

Most of the patients (60%) had no history of addiction (Fig. 7).

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| ASCENDING COLON | 7 | 14% |
| HEPATIC FLEXURE | 5 | 10% |
| TRANSVERSE COLON | 6 | 12% |
| SPLENIC FLEXURE | 3 | 6% |
| DECENDING COLON | 4 | 8% |
| SIGMOID COLON | 12 | 24% |
| RECTO SIGMOID JUNCTION | 5 | 10% |
| RECTUM | 8 | 16% |
| TOTAL | 50 | 100% |

***Figure 8***

Most common site was the sigmoid colon (24%) followed by the rectum (16%) and the ascending colon (14%) (Fig. 8).

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| RT HEMICOLECTOMY | 10 | 20% |
| EXT RT HEMICOLECTOMY | 4 | 8% |
| TRANSVERSE COLECTOMY | 4 | 8% |
| LEFT HEMICOLECTOMY | 7 | 14% |
| EXTENDED LEFT HEMICOLECTOMY | 5 | 10% |
| SIGMOID COLECTOMY | 7 | 14% |
| APR | 7 | 14% |
| LAR | 6 | 12% |
| TOTAL | 50 | 100% |

***Figure 9***

List of the various surgical procedures done throughout this period of study (Fig. 9).

| PATIENTS | MEAN | STD DEV | MINIMUM | MAXIMUM | MEDIAN |
|---|---|---|---|---|---|
| 50 | 119.3 | 37.14 | 39 | 180 | 112.33 |

***Figure 10***

Distribution of follow-up period in days was 119 days (Fig. 10).

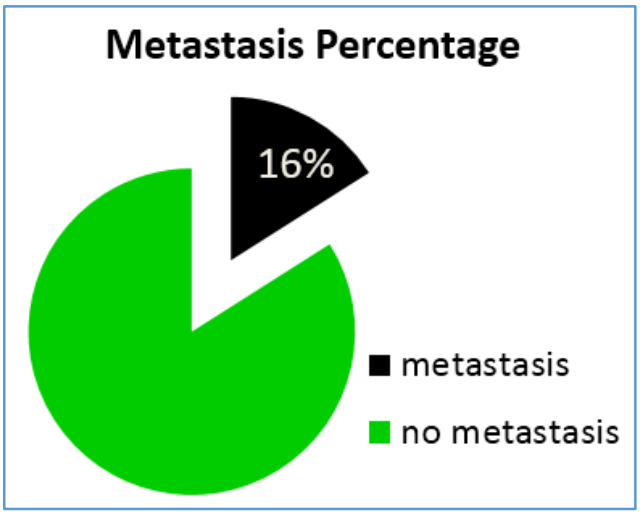


***Figure 11***

16% of the cases had metastasis at the end of the follow-up period (Fig. 11).

| | Number of patients | Patients with metastasis |
|---|---|---|
| Stage 2 ( 2 a,b,c) | 7 | 0 |
| Stage 3 ( 3 a,b,c) | 43 | 8 |

***Figure 12. Relationship of post-operative Staging with eventual development of Metastasis***

Metastasis was seen in patients with higher stage of the disease. Chi-square equals 0.296 with 1 degree of freedom. The two-tailed p-value equals 0.58, the result was not significant (Fig. 12).

| | CASES | METASTASIS |
|---|---|---|
| RESIDUAL TUMOR | 3 | 3 |
| NO RESIDUAL TUMOR | 47 | 5 |

***Figure 13. Relation of Presence of residual Tumour following surgery with Metastasis***

Metastasis was seen in every case with evidence of residual tumour. Chi-square equals 4.37 with 1 degree of freedom. The two-tailed p-value equals 0.0365. The association is considered statistically significant at p-value of <0.05 (Fig. 13).

| | CASES | METASTASIS |
|---|---|---|
| WITH LV INVASION | 16 | 4 |
| WITHOUT LV INVASION | 34 | 4 |

***Figure 14. Relation of Lymphovascular Invasion with Metastasis***

Metastasis was more frequent in patients with lymphovascular invasion. Chi-square equals 0.353 with 1 degree of freedom. The two-tailed p-value equals 0.55, association is not statistically significant (Fig. 14).

| | CASES | METASTASIS |
|---|---|---|
| LESS THAN 5CM | 25 | 6 |
| MORE THAN 5CM | 25 | 2 |

***Figure 15. Relation of Size of Tumour with Metastasis***

There is no relation of size of tumour with metastasis. Chi-square equals 0.87 with 1 degree of freedom. The two-tailed p-value is 0.35 (Fig. 15). The association is not statistically significant.

| HISTOLOGICAL SUBTYPE | CASES | METASTASIS | PERCENTAGE |
|---|---|---|---|
| WELL DIFFERENTIATED ADENOCARCINOMA | 11 | 0 | 0 |
| MODERATELY DIFFERENTIATED ADENOCARCINOMA | 29 | 3 | 10.3% |
| POORLY DIFFERENTIATED ADENOCARCINOMA | 10 | 5 | 50% |

***Figure 16. Relation of Histological Subtype with Metastasis***

Poorly differentiated tumours were associated with the highest risk of metastasis (50%) (Fig. 16).

| CEA | CASES | METASTASIS |
|---|---|---|
| CEA <5 | 13 | 1 |
| CEA >5 | 37 | 7 |

***Figure 17. Relation of High pre-operative CEA with Metastasis***

Preoperative CEA level > 5 IU was associated with high risk of metastasis. Chi-square equals 0.14 with 1 degree of freedom. The two-tailed p-value equals 0.701. The association was not statistically significant (Fig. 17).

| | CASES | METASTASIS |
|---|---|---|
| LOW GRADE ( G 1+2) | 36 | 4 |
| HIGH GRADE (G 3) | 14 | 4 |

***Figure 18. Relation of Grade of Tumour with Metastasis***

Metastasis was more commonly associated with high-grade tumours. Chi-square equals 0.701 with 1 degree of freedom. The two-tailed p-value equals 0.402. The association is not statistically significant (Fig. 18).

| | CASES | METASTASIS |
|---|---|---|
| MSI-H | 13 | 1 |
| MSI-L | 37 | 7 |
| TOTAL | 50 | 8 |

***Figure 19. Relation of Microsatellite Instability with Metastasis***

MSI-L was associated with poor prognosis and higher risk of metastasis. Chi-square equals 0.14 with 1 degree of freedom. The two-tailed p-value is 0.701. The association was not statistically significant (Fig. 19).

## DISCUSSION

In this study, 50 patients with colorectal carcinomas were chosen who did not have any metastasis nor were previously operated. Large scale study was not possible due to lack of resource constraints. All cases were finally diagnosed after histopathological examination.

The mean age of this study was 51 years, which was 10 years early than the average age (60 - 80 years) as per the western data.[6] In this study 20% of the patients were aged less than 40 years, despite none of the patients having any positive family history of colorectal cancers. It is a rather alarming finding when compared to the age adjusted incidence rates in the western countries. The probable cause of this shifting to the younger side could be due to limited number of cases, geographical and environmental factors as well.

In this study, majority (56%) of the patients were females. The female: male ratio was 1.2: 1, despite colorectal malignancies being more common among men.[6]

Among the symptoms 64% patients had complaints of alteration of bowel habit, bleeding per rectum was associated with 60% of the cases. Loss of weight was associated with 58% of the patients.

In 6% of the cases past history of malignancies could be elucidated which were breast carcinoma (2%), ovarian carcinoma (2%) and prostate (2%) carcinoma. Association of breast cancer with HNPCC and mismatch repair genes can explain such an occurrence.[7] Younger men with colorectal carcinomas have been found to be more susceptible to prostate cancers.[8] Large scale studies are still pending to stamp in favour of such an association.

Preoperatively, the most common site of malignancy were the sigmoid colon (24%) followed by rectum (16%) and ascending colon (14%). In the majority, preoperative biopsy was suggestive of moderately differentiated adenocarcinoma (58%).

Based on the operative findings and post-operative histology, the patients were followed up for an average of 119 days with the provision of adjuvant chemoradiotherapy during this period. Routine investigations and cross-sectional imaging was done during this period.

In 16% of the patients, metastasis was found during the follow-up period.

We tried to identify the relationship between preoperative staging of the patient and the final outcome. It was found that all the cases of metastasis were associated with the advanced stage (Stage 3) of the disease.[9,10] Thus, it

signifies the importance of staging in terms of prognostic significance.

In case of presence of residual tumour following the primary surgery the incidence of metastasis was 100% and when compared to the patients with absence of any residual tumour using the Chi-square test the p-value was 0.036 and was therefore statistically significant. Therefore, residual tumour after a definitive therapy is an adverse prognostic factor.[11]

Incidence of metastasis was more common (25%) among the patients with histopathological finding of lymphovascular invasion, but the association was not statistically significant**.** Presence of lymphovascular invasion indicates aggressive behaviour and hence is an adverse factor in terms of survival.[12,13]

Size of the tumour had nothing to do with the final outcome of the patient.[14]

It was seen that patients with well-differentiated adenocarcinoma were not that aggressive in nature, but patients with moderately (10.3%) and poorly differentiated adenocarcinoma (50%) were associated with risk of metastasis. Poorly differentiated carcinomas like mucinous and Signet ring adenocarcinoma frequently have metastatic disease and also at multiple sites when compared to classical adenocarcinoma.[15]

Metastasis was more among the patients with higher grade (Grade 3) of the tumour (28.57%). Therefore, grading of tumour has been considered as a stage independent prognostic factor.[16]

Preoperative Carcinoembryonic Antigen (CEA) levels more than 5 IU was associated with a higher risk of metastasis (18.9%), but the association was not statistically significant. The Surveillance Epidemiology and End Results (SEER) database in 2004 showed the increased risk of mortality with elevated preoperative CEA levels.

Assessment of Microsatellite instability status in these sporadic cases showed that the patients with MSI-H were associated with better prognosis and the patients with MSI-L were associated with poor prognosis, as the rate of metastasis was high (18.9%). Therefore, assessment of MSI status in sporadic cancers carries immense significance in terms of prognostication, deciding the adjuvant therapy and is used in further clinical decision making.[17,18]

## CONCLUSION

Thus, assessment of certain factors both pre-operatively and post-operatively can guide us towards prediction of the final outcome of the patient in terms of complete cure or the risk of recurrence or metastasis. Patients presenting with such poor prognostic factors should be diagnosed early with the help of different screening investigations and treated aggressively considering the outcome which should include an adequate surgery followed by newer modalities of adjuvant therapy that can combat this situation.

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