JMSCR Vol||05||Issue||12||Page 31475-31486||December 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i12.41

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Co-Relation between CEA Level and Different Stages of Colorectal Carcinoma

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Abstract

Introduction: *Colorectal carcinoma is the third most common cancer in men and second in women worldwide. Incidence rates per 100,000 in India for males is 4.3/100000 and for females is 3.4/100000. Levels of various substances in blood can help act as tumor marker for the detection, staging and prognosis of the patients.CEA levels are elevated in 60-90% of patients with colorectal carcinomas. Despite its lack of specificity it can help in making clinical decisions and assessing therapy response.*

Aims

1 .To assess if preoperative CEA level an independant indicator of severity of colorectal cancer(as indicated by TNM staging)

2. To find out percentage of cases showing elevation of CEA Levels in different stages of colorectal carcinoma

Materials and Methods: *We conducted a study on all patients admitted in Department of surgery in Government medical college, Thiruvananthapuram over a period of 20 months with diagnosis of colorectal carcinoma who already had a baseline CEA levels done as a part of workup. Smokers were included in the study but were considered as having high CEA levels only when the level was more than 5ng/ml. Data was entered in structured proforma and correlated with CEA levels and statistically analysed using Chi square test and Mann whitney U test.*

Results: *Out Of 78 patients studied only 29(37%) had elevated CEA Levels irrespective of the stage of the disease. majority (56%) presented with bleeding per rectum. most common blood group affected was O+ve. CECT detected lesions in 95% cases. Most common histopathological pattern was well differentiated adenocarcinoma. On analysis using Mann Whitney U test it was found that CEA levels rose progressively with the stage of the disease but p-value was found to be 0.066.*

Conclusion: *From this study it was found that colorectal carcinoma was predominantly a disease of people aged above 50 yrs of age, majority (56%) presented with bleeding per rectum as main symptom and inferred that there is no correlation between CEA levels and different stages of colorectal carcinoma. Hence CEA levels cannot be used to predict the severity of colorectal carcinoma as indicated by TNM Staging.*

Keywords: *Colorectal carcinoma, CEA (Carcinoembryonic antigen).*

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide. The age adjusted incidence rates of CRC in India are close to the lowest rates in the world. Hospital based and population based data shows that the incidence rates for rectal cancer is higher than colon cancer in India. Incidence rates in India for males is 4.3/100000 & for females is 3.4/100000[(1)]. The peak incidence for the development of colorectal cancer is 60 years of age. This suggests a 10-year time span for the progression of an adenomatous polyp to a cancer. [(2)]

Numerous epidemiological associations have been associated with development of carcinoma colon. Cigarette smoking has an increased risk of colonic adenomas, especially after more than 35 years of use[(3)].

It is important to recognize the increased risk for cancer in patients with hereditary cancer syndromes who present with polyps but by far the most common form of colorectal cancer is sporadic in nature, without an associated strong family history.

The small diminutive polyps are usually regarded as benign in nature with no neoplastic potential. But histologic appearance of serrated adenomas of these polyps are seen to be associated with the microsatellite instability characteristic of defects in DNA repair mechanisms.[(4)]

Likewise adenocarcinoma colon which is the main histopathological type of colon cancer, has a variant of mucinous adenocarcinoma which when compared with nonmucinous colon cancers are found to present at a more advanced stage and with an overall poorer prognosis[(5)]

The signs and symptoms of colon cancer are mainly nonspecific and depends on the location of the tumor as well as the extent of constriction of the lumen caused by the carcinoma in the colon. During the past several decades, the incidence of cancer in the right colon has increased in comparison to cancer arising in the left colon and rectum.[(6)]

There are many modalities for detection and prognostication of colorectal carcinomas. Computed tomography (CT) is commonly employed in the evaluation of patients with abdominal complaints and primarily in the detection of extraluminal disease. A standard CT scan is relatively insensitive for the detection of intraluminal lesions.[(7)]

Virtual colonoscopy is a new radiologic technique that is designed for early evaluation of virtual colonoscopy and its accuracy may approach that of colonoscopy for detection of lesions 1 cm in diameter or greater. Ultrasound can reliably differentiate most benign polyps from invasive tumors based upon the integrity of the submucosal layer and may also prove useful for early detection of local recurrence after surgery.[(8)]

Tumor markers found in body fluids, particularly blood and urine, have the greatest potential for clinical application because of the ease of access to these fluids for analysis and because repeated sampling allows in vivo monitoring of the malignancy for such features as disease progre-ssion or recurrence, metastasis, and response to therapy.[(9)]

Tumor markers in serum like CEA, ornithine decarboxylase, urokinase have been proposed, but none has yet proven sensitive or specific for detection, staging, or predicting prognosis of colorectal carcinoma. Carcinoembryonic antigen (CEA) may be elevated in 60 to 90% of patients with colorectal cancer. Many practitioners follow serial CEA levels after curative-intent surgery for detection of early colorectal cancer recurrence. However, this tumor marker has no proven no survival benefit[(10)]. So this study has been done to analyse the variation in CEA levels with different stages of colorectal carcinoma.

Materials and Methods

Background and Objectives

A thesis on colorectal carcinoma was opted for as it is a very commonly encountered carcinoma in the local population.

Objective

Primary- To assess whether pre-operative CEA level is an independent indicator of severity of colorectal cancer (as indicated by TNM staging)?

Secondary- To find out percentage of cases showing elevation of CEA levels in different stages

Type of Study: Descriptive study design

Settings of the Study: Department of Surgery, Department of pathology & Department of Surgical gastroenterology of Government Medical College, Trivandrum.

Duration of Study: 20 months (march2011-nov2012)

Study Tool & Variables: Study tool includes a structured proforma which includes variables like sociodemographic variables, family history, colonoscopic findings, CEA levels, CT staging, Family History, smoking/alcoholic history and other variables relevant to colorectal carcinoma.

Sample Size

Sample size is calculated using the formula

N= 3.96PQ/L X L

Where

P=proportion of cases that are positive

Q=100-P

L=20% of P

Now here P=59% (4)

So q=41

Hence L=11.8

So applying these values in the equation the sample size comes as 69 cases

CEA Level Measurement

Level of CEA assessed at ACR lab at medical college, Trivandrum.

Machine used is Access-2 by Beckman Coulter.

20 microlitres of blood needed.

Placed in a couvette & centrifuged.

Machine is self calibrated and readings obtained within 5 min.

Statistical Analysis

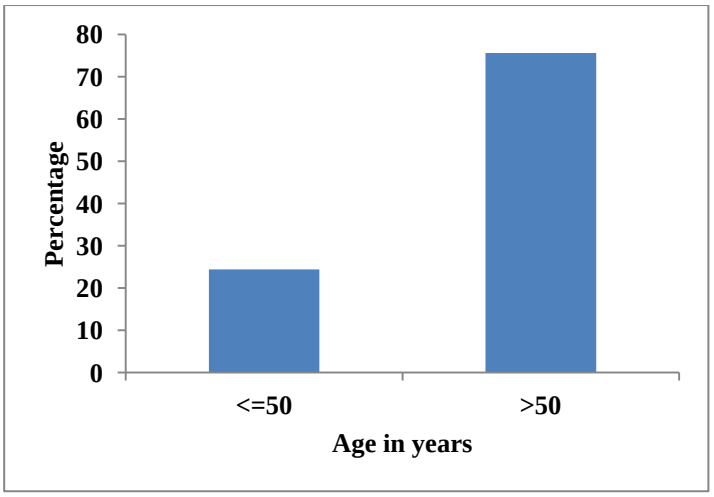
1. Chi square test
2. Mann- Whitney U test
3. Analysis of CEA levels

Observations and Results

Patients with Colorectal Carcinoma admitted in Medical College Hospital Thiruvanant-hapuram, were studied from April 2011 to November 2012. Total number cases studied were 78.

Age

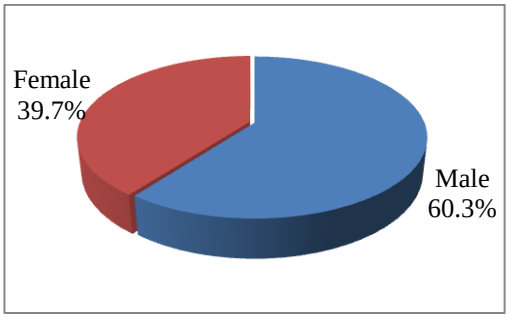
Age	Frequency	Percent
<=50	19	24.4
>50	59	75.6
Total	78	100.0



Of all the patients admitted with colorectal carcinoma, 19 were aged below 50 years whereas 59 patients were over the age of 50. From the available data of patients admitted at MCH, Trivandrum, it is clear that 75% of patients affected with this disease are aged over 50.

Sex

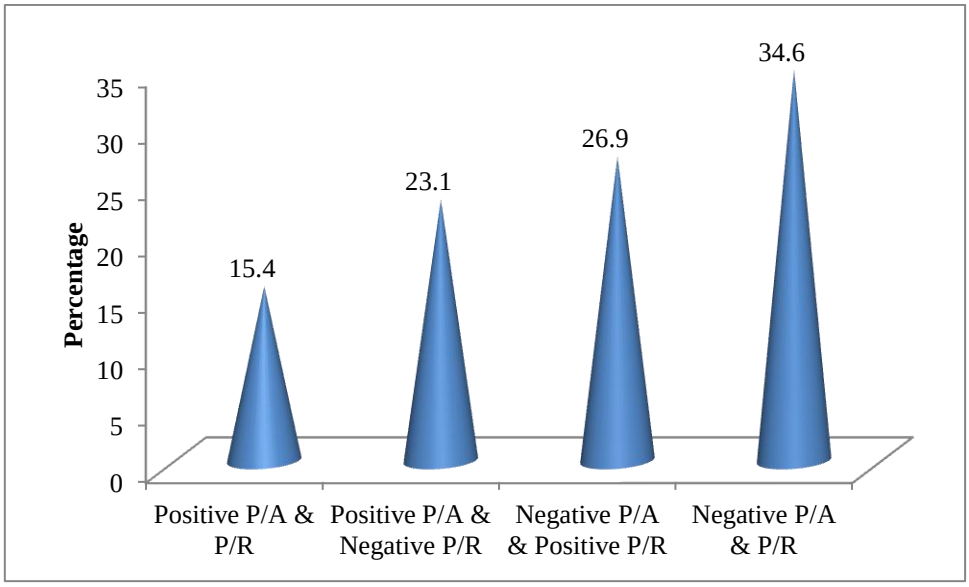
Sex	Frequency	Percent
Male	47	60.3
Female	31	39.7
Total	78	100.0



Of the 78 patients affected with colorectal carcinoma, majority were males (60%). In contrast females were affected only in 40% of the cases. Thus the prevalence of the disease as per this study translates into a male: female ratio of 3:2.

Examination Findings

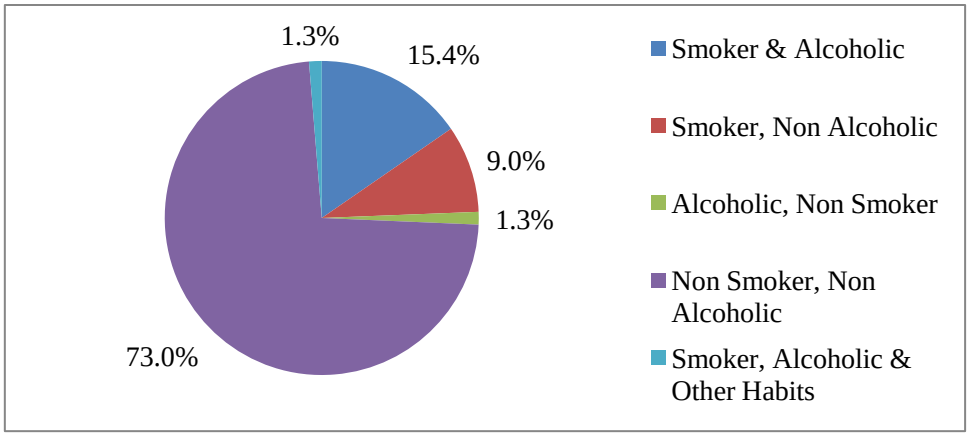
Examination Findings	Frequency	Percent
Positive P/A & P/R	12	15.4
Positive P/A & Negative P/R	18	23.1
Negative P/A & Positive P/R	21	26.9
Negative P/A & P/R	27	34.6
Total	78	100.0



Paradoxically of all the patients suffering from this disease, most of them only had symptoms. Clinical evaluation was neutral in upto 35% of patients. Of the remaining 65% of the patients 27% had only a positive P/R finding in contrast with 23% who had only a P/A finding. 15% of the patients had both P/A & P/R positive findings. Thus it is inferred that the most consistent finding is a positive per rectal examination which is positive in upto 42% of the patients in contrast to abdominal examinations which are positive only in 38% of the patients. This is closely followed by negative examination findings seen in 35% of individuals.

Habits

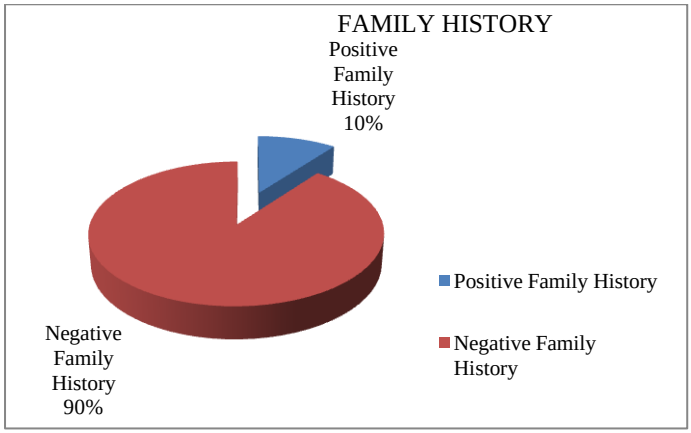
Habits	Frequency	Percent
Smoker & Alcoholic	12	15.4
Smoker, Non Alcoholic	7	9.0
Alcoholic, Non Smoker	1	1.3
Non Smoker, Non Alcoholic	57	73.1
Smoker, Alcoholic & Other Habits	1	1.3
Total	78	100.0



15% of the patients suffering from this disease were both smokers as well as alcoholics. Another 1% had other bad habits (like betel nut chewing, drug abuse) in addition to smoking & alcoholism. 9% were solely smokers & 1% of the patients were solely alcoholics. Paradoxically 73% of the patients were neither smokers nor alcoholics. Thus patients having colorectal carcinoma were smokers (26%), alcoholics (18%). Since 73% of the patients had no such habits it is to be interpreted that smoking or alcoholism cannot be considered as a causative factor in colorectal carcinoma.

Family History

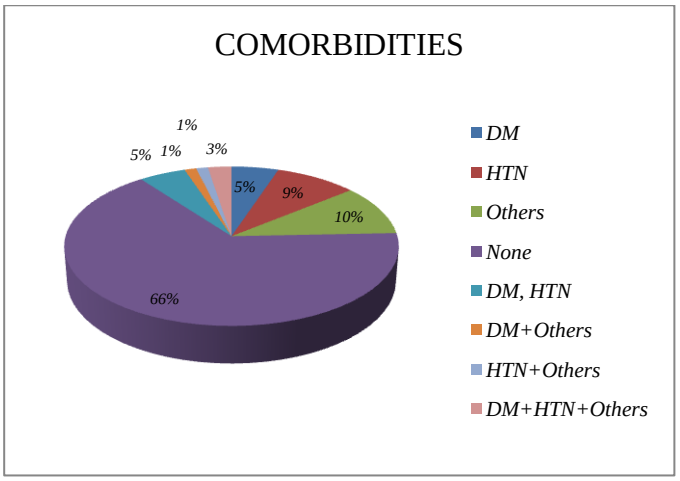
FAMILY HISTORY	Frequency	Percent
Positive Family History	8	10.3
Negative Family History	70	89.7
Total	78	100.0



Of all the admitted patients only 8 had a positive family history. Rest of the 70 patients had no history of any malignancy in the family. Thus from this study it can be concluded that sporadic cases of colorectal carcinoma were more common (90%) as compared to familial carcinoma(10%). So colorectal carcinoma occurs in a ratio of 9:1 as far as prevalence of sporadic to familial cases is concerned.

Comorbidities

Comorbidities	Frequency	Percent
DM	4	5.1
HTN	7	9.0
Others	8	10.3
None	51	65.4
DM, HTN	4	5.1
DM+Others	1	1.3
HTN+Others	1	1.3
DM+HTN+Others	2	2.6
Total	78	100.0

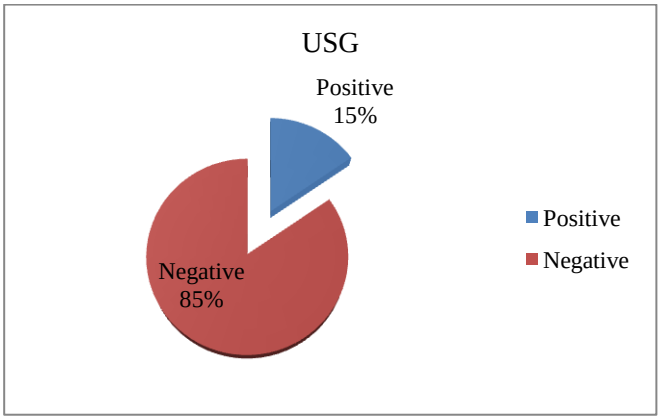


Comorbidities were classified into 3 categories for this study. Those patients who have Diabetes Mellitus (DM). Those with Hypertension & finally those with any other co-morbidity (inclusive of CAD, CVAetc).

Of these Hypertension was more commonly associated with colorectal carcinoma (18%) as compared to Diabetes Mellitus (13%). Interestingly a whopping 66% of the patients had no co-morbidity at all.

USG

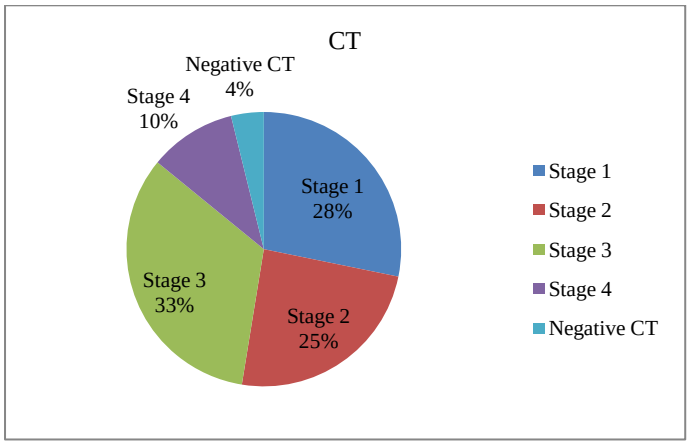
USG	Frequency	Percent
Positive	12	15.4
Negative	66	84.6
Total	78	100.0



When suspicious patients were evaluated further with the help of an ultrasound it was beneficial in only 15% of the patients. 85% of the patients had no detectable findings on ultrasound.

CT Findings

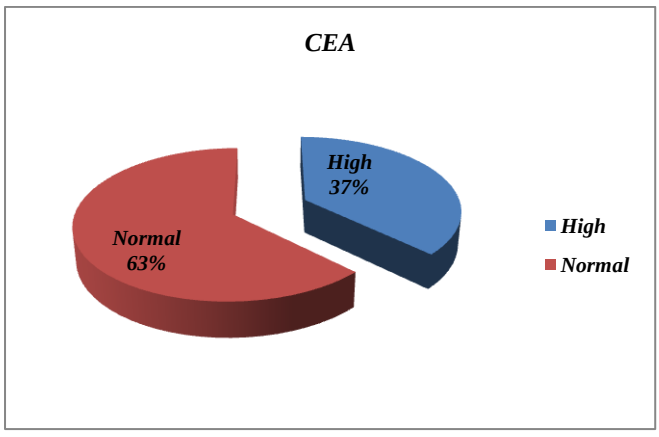
CT	Frequency	Percent
Stage 1	22	28.2
Stage 2	19	24.4
Stage 3	26	33.3
Stage 4	8	10.3
Negative CT	3	3.8
Total	78	100.0



When CT was used as the tool for evaluation it was found that of the 78 patients with carcinoma, 4 had lesions that was not detectable on CT. Of the remaining 74 patients, the stages found as on CT were 28% stage I, 25% stage II, 33% stage III & 10% stage IV. Thus as per the CECT findings the most common stage of colorectal carcinoma in the local population was stage III.

CEA

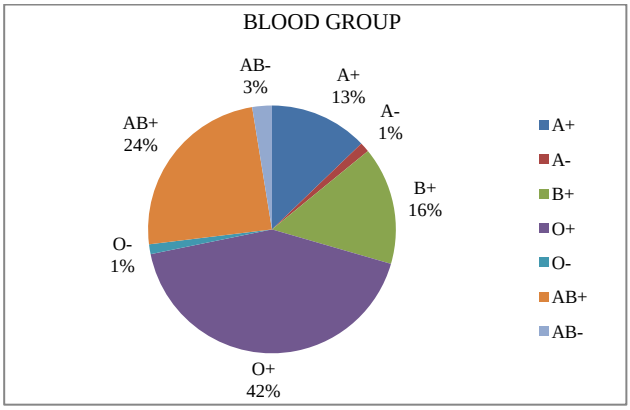
CEA	Frequency	Percent
High	29	37.2
Normal	49	62.8
Total	78	100.0



Of all the patients admitted with colorectal carcinoma only 37% of the patients had an elevated CEA level. This value is irrespective of the stage of the disease.

Blood Group

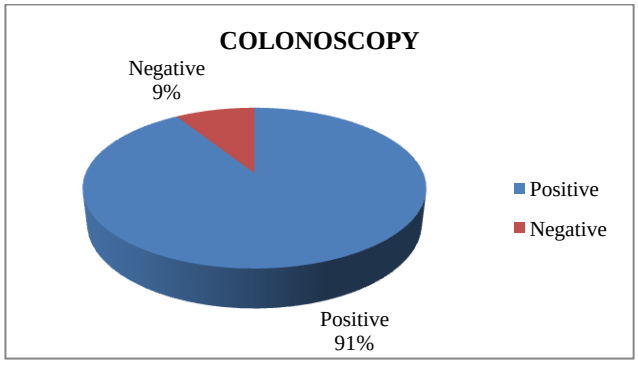
BLOOD GROUP	Frequency	Percent
A+	10	12.8
A-	1	1.3
B+	12	15.4
O+	33	42.3
O-	1	1.3
AB+	19	24.4
AB-	2	2.6
Total	78	100.0



Of all the blood groups group O is the most common in the world (63%-95%) in various populations of the world. Of the people who developed colorectal carcinoma only 43% had O blood group- 42% O+ & 1% O-. The other blood groups in order of frequency were- AB+(24%), B+(16%), A+(13%) & all negative groups combined together(5%).

Colonoscopy

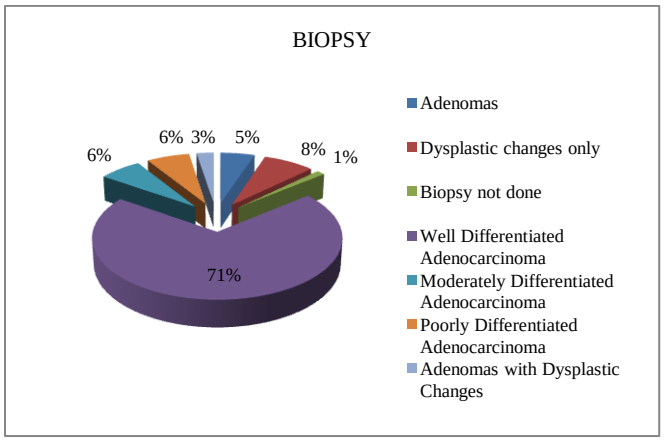
Colonoscopy	Frequency	Percent
Positive	71	91.0
Negative	7	9.0
Total	78	100.0



When colonoscopy was used as a diagnostic tool in any patient with signs/symptoms of colorectal cancer it was found that the results were positive in >90% of patients. This is in stark contrast to USG abdomen that yielded positive results only in 15% of the patients. Thus it is prudent to say that both CECT & Colonoscopy are high yield investigations when evaluating a patient with suspected colorectal carcinoma.

Histopathology Findings

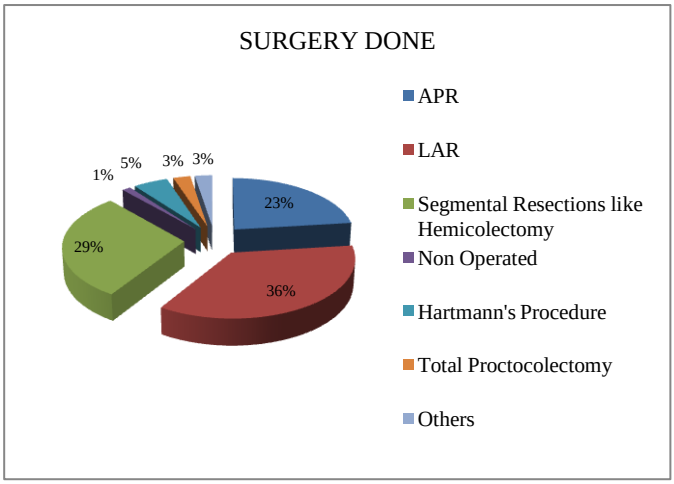
BIOPSY	Frequency	Percent
Adenomas	4	5.1
Dysplastic changes only	6	7.7
Biopsy not done	1	1.3
Well Differentiated Adenocarcinoma	55	70.5
ModeratelyDifferentiated Adenocarcinoma	5	6.4
Poorly Differentiated Adenocarcinoma	5	6.4
Adenomas with Dysplastic Changes	2	2.6
Total	78	100.0



The most common biopsy finding after a colonoscopy was a well differentiated adenocarcinoma (71%). Adenocarcinoma in total (including moderately & poorly differentiated varities) constituted 83% of the cases. All other histological varities formed only a minor fraction of the cases ranging from 1-6%.

Surgery Done

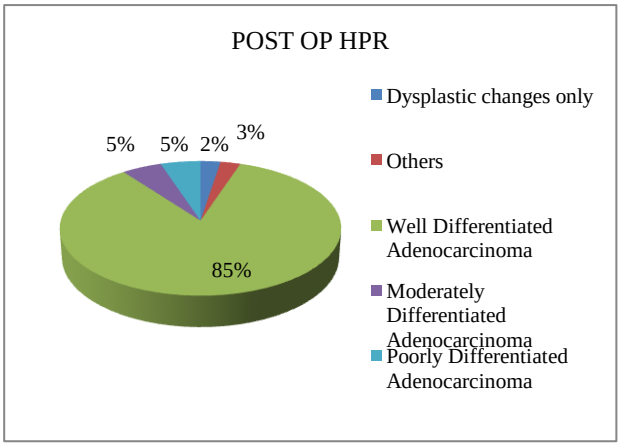
SURGERY DONE	Frequency	Percent
APR	18	23.1
LAR	28	35.9
Segmental Resections like Hemicolectomy	23	29.5
Non Operated	1	1.3
Hartmann's Procedure	4	5.1
Total Proctocolectomy	2	2.6
Others	2	2.6
Total	78	100.0



Of the patients who underwent surgery the most common procedures were LAR (36%), segmental resections (29%) & APR(23%). Other surgeries formed only a fragment of cases ranging from 1-5%.

Post Operative Histopathologic Findings

POST OP HPR	Frequency	Percent
Dysplastic changes only	2	2.6
Others	2	2.6
Well Differentiated Adenocarcinoma	66	84.6
Moderately Differentiated Adenocarcinoma	4	5.1
Poorly Differentiated Adenocarcinoma	4	5.1
Total	78	100.0

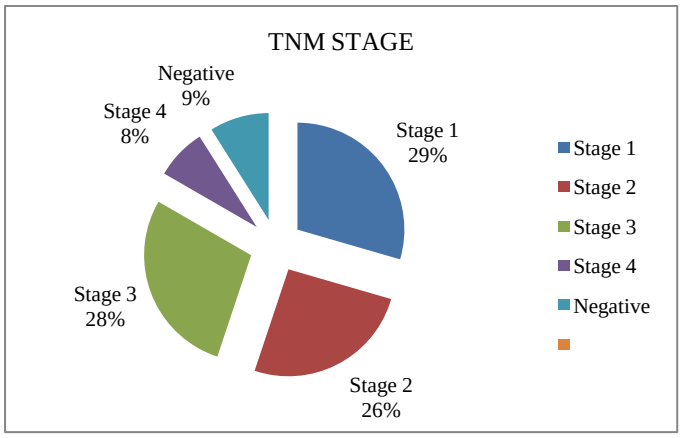


Once post operative HPR results were available it was noted that well differentiated adenocarcinoma were even more common(85%) that detected by pre operative colonoscopy based biopsy reports (71%).

In fact when overall prevalence of adenocarcinoma was taken into account it was found that adenocarcinoma formed a whopping 95% of cases leaving very little room for other histo pathological varieties of carcinoma.

TNM Staging

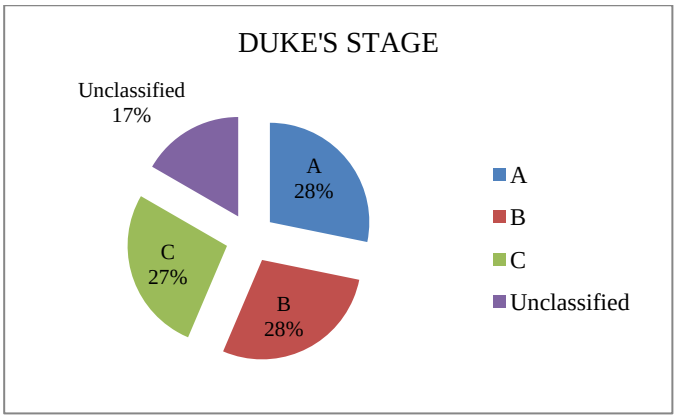
TNM STAGE	Frequency	Percent
Stage 1	23	29.5
Stage 2	20	25.6
Stage 3	22	28.2
Stage 4	6	7.7
Negative	7	9.0
Total	78	100.0



Based on postoperative HPR it was found that the most common stage of colorectal carcinoma is stage I (29%), followed closely by stage III(28%). Stage II carcinomas constituted 26% and stage IV constituted 8% of the cases. Interestingly 9% of the cases showed no evidence of carcinoma on postoperative histopathological analysis.

Duke's Staging

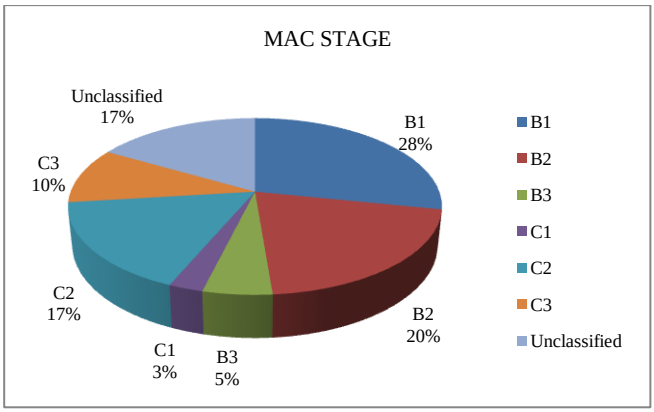
Duke's Stage	Frequency	Percent
A	22	28.2
B	22	28.2
C	21	26.9
Unclassified	13	16.7
Total	78	100.0



When the postoperative histopathology was extrapolated to DUKE's staging the prevalence of carcinoma colon detected was-stage A & B (28% each),stage C(27%). 17% of the patients could not be classified as per the DUKE'S staging.

MAC Staging

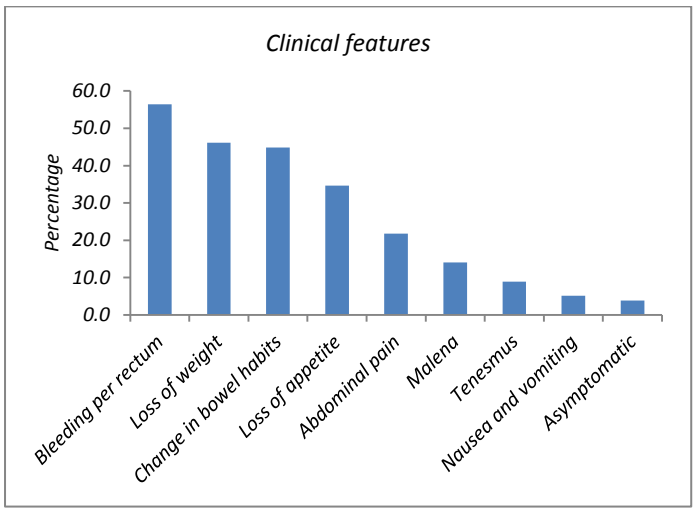
MAC STAGE	Frequency	Percent
B1	22	28.2
B2	16	20.5
B3	4	5.1
C1	2	2.6
C2	13	16.7
C3	8	10.3
Unclassified	13	16.7
Total	78	100.0



When similar extrapolation of postoperative HPR was done to MAC staging it was found that stage B was the commonest type-53%(B1-28%,B2-20%, B3-5%). Stage C constituted 30% of the cases (C1-3%, C2-17%,C3-10%). None of the tumors could be grouped under stage A whereas 17% remained unclassified as per the MAC staging.

Clinical Presentation

Clinical presentation	Frequency	Percent
Malena	11	14.1
Asymptomatic	3	3.8
Change in bowel habits	35	44.9
Bleeding per rectum	44	56.4
Abdominal pain	17	21.8
Loss of weight	36	46.2
Nausea and vomiting	4	5.1
Tenesmus	7	9.0
Loss of appetite	27	34.6

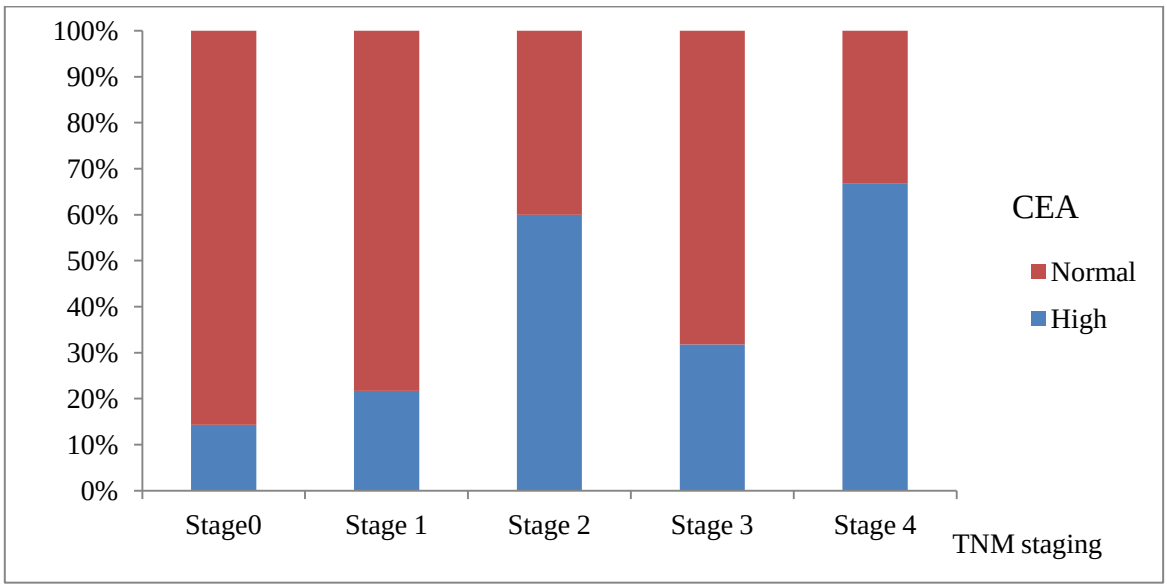


The most common symptom in a patient with colorectal carcinoma was found to be bleeding per rectum (56%). Loss of weight and change in bowel habits were the next most common symptoms seen in 46 and 45% of the patients respectively. Loss of appetite, abdominal pain, maleana, tenesmus and nausea and vomiting completes the spectrum of common clinical features in that order. 4% of the patients with colorectal carcinoma were found to be asymptomatic.

TNM Staging and CEA Levels

TNM staging	CEA				Total	
	High		Normal			
	N	%	N	%	N	%
Stage0	1	14.3	6	85.7	7	100.0
Stage 1	5	21.7	18	78.3	23	100.0
Stage 2	12	60.0	8	40.0	20	100.0
Stage 3	7	31.8	15	68.2	22	100.0
Stage 4	4	66.7	2	33.3	6	100.0
Total	29	37.2	49	62.8	78	100.0

Mann whitney U test P = 0.066



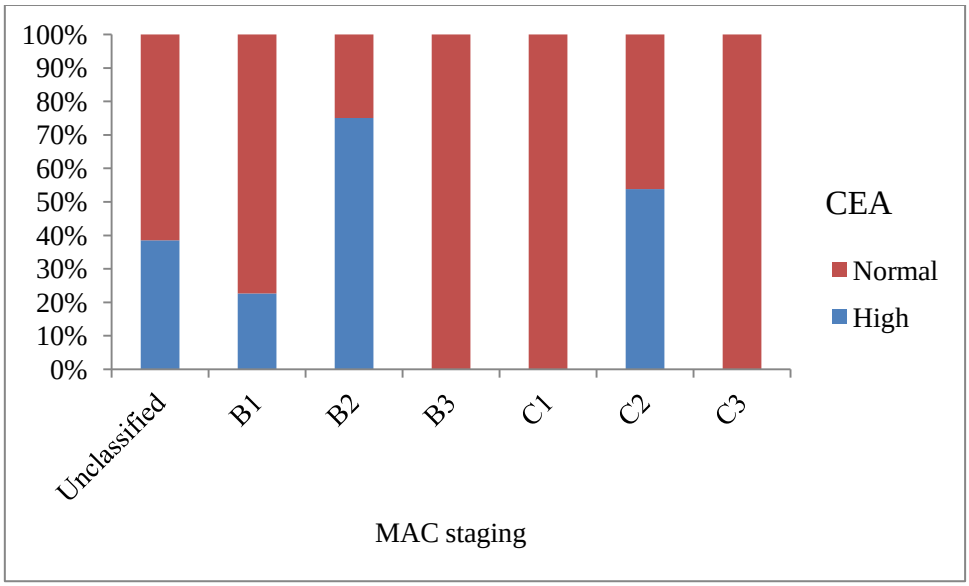
When CEA levels were correlated with different stages of colorectal carcinoma, it was found that the levels of CEA rose progressively with each stage of colorectal carcinoma. For studying this correlation Mann-Whitney U test was used. The p-value for the statistical analysis was 0.066. Since the p-value is greater than 0.05, it is to be inferred, that though CEA levels rise progressively with each stage of colorectal carcinoma , the value as a whole is statistically insignificant. Hence CEA level cannot be used to predict the severity of colorectal carcinoma as indicated by the TNM staging.

CEA level was found to be positive in 21% of stage I, 60% of stage II, 32% of stage III and 67% of stage IV colorectal carcinomas.

MAC Staging and CEA Levels

MAC staging	CEA				Total	
	High		Normal			
	N	%	N	%	N	%
Unclassified	5	38.5	8	61.5	13	100.0
B1	5	22.7	17	77.3	22	100.0
B2	12	75.0	4	25.0	16	100.0
B3	0	.0	4	100.0	4	100.0
C1	0	.0	2	100.0	2	100.0
C2	7	53.8	6	46.2	13	100.0
C3	0	.0	8	100.0	8	100.0
Total	29	37.2	49	62.8	78	100.0

Mann whitney U test P = 0.849

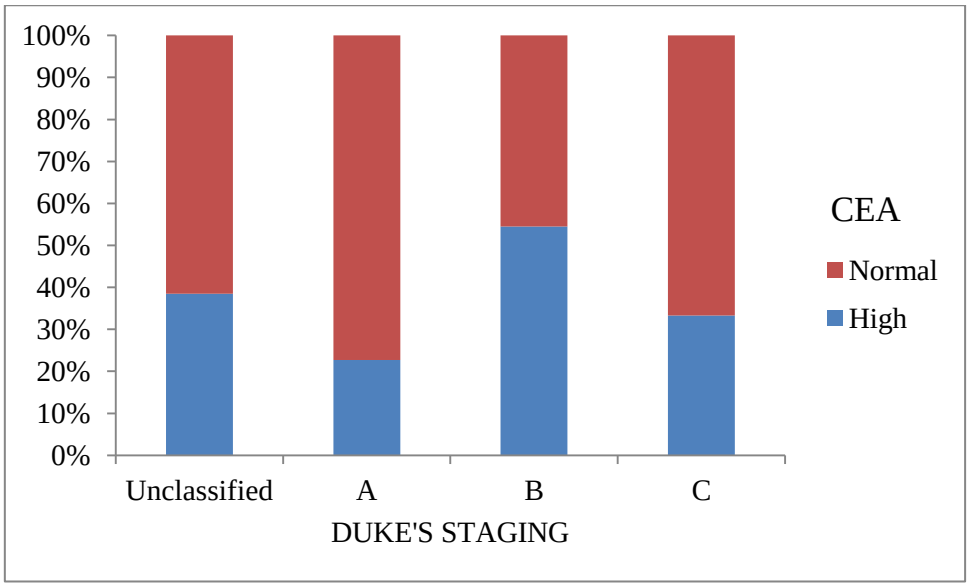


When CEA levels were correlated with different stages of the MAC system, no definite pattern was noted between CEA values and the different stages. Moreover the p-value using the Mann-Whitney U test was 0.849. Thus this correlation is hardly of any statistical significance.

Duke's Staging and CEA Levels

DUKE'S STAGE	CEA				Total	
	High		Normal			
	N	%	N	%	N	%
Unclassified	5	38.5	8	61.5	13	100.0
A	5	22.7	17	77.3	22	100.0
B	12	54.5	10	45.5	22	100.0
C	7	33.3	14	66.7	21	100.0
Total	29	37.2	49	62.8	78	100.0

χ^2 =4.950 df= 3 p= 0.175



Similar to the MAC staging, no correlation was found between CEA levels or the DUKE'S staging. The only difference was that Chi-square test was used for analysis. P-value was found to be 0.175, thus rendering the exercise, statistically insignificant.

Conclusion

From the study hereby conducted the following results were inferred

1) Colorectal carcinoma is predominantly a disease of people above the age of 50. They form the major burden of disease contributing to 75% of the cases.
2) The male to female ratio for colorectal carcinoma is 3:2.
3) The most common clinical presentation in colorectal carcinoma is bleeding per rectum(56%) followed by loss of weight and change in bowel habits.
4) When patients with suspicious symptoms were subjected to clinical evaluation a positive per rectal finding was seen in 42% of the cases. Abdominal findings were positive in 38% of the cases whereas clinical findings were inconclusive in 35% of the cases.
5) Both smoking and alcoholism are not strongly related to colorectal carcinoma as they are seen only in 26 and 18% of the cases respectively.
6) Hypertension as a comorbidity was present in 18% of the cases with colorectal carcinoma whereas diabetes was seen in 13%.
7) The most common blood groups in patients with colorectal carcinoma were as follows O+ve (42%), AB+ve (24%) B+ve (16%),A+ve (13%) and all negative groups (5%).
8) When the patients were subjected to imaging/invasive investigations it was found that CECT abdomen was able to detect lesions in upto 95% of the cases whereas colonoscopy showed a positive finding in approximately 90% of the patients. Paradoxically USG yielded a positive finding in only 15% of the cases.
9) Irrespective of the stage of the disease CEA levels were positive in only 37% of the cases of colorectal carcinoma.
10) The most common histological type of colorectal carcinoma is a well differentiated adenocarci-noma. Colonoscopic biopsy demonstrated this in 71% of the cases whereas on postoperative HPR a well differentiated adenocarci-noma was seen in upto 85% of the cases.
11) The surgeries mainly performed for colorectal carcinomas are – LAR (36%), segmental resections like colectomy (29%) and APR (23%).

12) The most common stage of colorectal carcinoma with which patients presented to this institution was the stage I colorectal carcinoma (29%), followed closely by a stage III carcinoma.[TNM staging]
13) Most common stage of carcinoma based on DUKE'S staging is both stage A and B (28% each) whereas the most common type as per MAC staging was stage B(53%).
14) When CEA levels were correlated with different stages of colorectal carcinoma (TNM staging) it was found that CEA levels rose progressively with each stage of the disease. But no such definitive pattern was noted when CEA levels were compared with DUKE'S or MAC staging. In all the 3 cases mentioned above the p-value was greater than 0.05 an hence statistically insignificant.

The primary objective was to assess the severity of colorectal carcinoma (as per the tnm staging) based on CEA levels. On analysis using the MANN WHITNEY U test it was found that CEA levels rose progressively with each stage of the disease but the p-value was found to be 0.066. Thus it is to be inferred that there is no correlation between CEA levels and different stages of colorectal carcinoma.

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