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EVALUATION OF MUCIN 1 EXPRESSION AND ITS CORRELATION WITH GRADING AND STAGING IN COLORECTAL CARCINOMA

By

Dr. KEZIA ANNA JACOB

Dissertation submitted to

BLDE (DEEMED TO BE UNIVERSITY)

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In partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

PATHOLOGY

Under the Guidance of

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LIST OF ABBREVIATIONS

MUC1	Mucin 1
CRC	Colorectal Cancer
EGFR	Epidermal Growth Factor Receptor
APC	Adenomatous Polyposis Coli
BRAF	B-Raf proto-oncogene, serine/threonine kinase
PTEN	Phosphatase and TENsin homolog deleted on chromosome 10
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CEA	Carcinoembryonic antigen
ASR	Age-standardized incidence rate
TNM	Tumor size, Lymph Node metastasis, Distant metastasis
H&E	Hematoxylin and Eosin
IHC	Immunohistochemistry
YRS	Years

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ABSTRACT

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related deaths globally, with approximately two million new cases and one million deaths reported in 2020. In India, CRC incidence has been increasing, particularly in the northeastern and southern regions, due to genetic factors, lifestyle, and environmental factors. Over 50% of cases are diagnosed at an advanced stage, limiting treatment options and worsening prognosis. Biomarkers such as Carcinoembryonic Antigen, CD133, and Mucin-1 (MUC1) play crucial roles in CRC detection. MUC1, a transmembrane glycoprotein, is linked to aggressive tumor behavior and poor prognosis. It was also mentioned that MUC1 expression was significantly correlated with advanced tumor grade, depth of invasion and lymph node metastasis. Hence, this study was undertaken to correlate MUC1 expression with the grading and staging of CRC.

OBJECTIVES

To evaluate MUC1 expression in tumor tissue of CRC and to correlate it with grading and staging of CRC.

MATERIAL AND METHODS

A hospital-based cross-sectional study was done on 40 specimens received in the Histopathology Section. Tumor tissue blocks on which diagnosis of CRC was made were evaluated for MUC1 expression and were correlated with grading and staging of CRC. Scoring of MUC1 positivity was done as Score 3+, 2+ and 1+ based on percentage of MUC1 positivity.

RESULTS

MUC1 expression showed Score 3+ positivity in 70% cases of moderately differentiated adenocarcinoma, 50% cases of well-differentiated adenocarcinoma and in all cases of poorly differentiated adenocarcinoma. A maximum number of cases showing score 3 MUC1 expression were in stage T3 and T4, amounting to 78.57% and 75%, respectively. Score 3+ MUC1 expression was noted in 60% of N0, 82% of N1 and 100% of N2. Maximum number of cases showing the depth of invasion in subserosa showed the highest score that is Score 3, amounting to 85.71% and Score 3 MUC1 expression was not observed in cases of CRC limited to submucosa.

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CONCLUSION:

MUC1 expression showed a positive correlation with tumor grading, staging, lymph node metastasis, and depth of invasion with more number of cases of poorly differentiated CRC, and higher stages of the tumor showed score 3 MUC1 expression in more cases. Also, cases of CRC showing Lymph node metastasis and depth of invasion in serosa and subserosa showed score 3 MUC1 expression in more cases. These findings suggest a role for MUC1 in the progression of colorectal cancer, suggesting a link of MUC1 expression with the aggressiveness of the tumor and poor prognosis.

KEYWORDS: Colorectal carcinoma, MUC1 expression, Staging, Grading

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INTRODUCTION

Colorectal cancer (CRC) is one of the foremost causes of cancer-related mortality globally. As per the 2020 data, approximately two million new cases of CRC have been reported, with nearly one million deaths attributed to the CRC.[1] In India, the incidence of CRC has shown an increasing trend over the years. The National Cancer Registry data from 1982 to 2010 reveal a steady rise in the annual percentage change, ranging from 0.9% to 5.8% for colon cancer and 2.7% to 9.8% for rectal cancer. The latest report, based on 27 population-based cancer registries, indicated an annual incidence rate of 5.36 per 100,000 population for colon cancer and 5.17 per 100,000 for rectal cancer in men and in women. The incidence rate for colon cancer was 4.3 per 100,000 population.[2]

The northeastern and southern regions of India have a much higher prevalence of colorectal cancer, potentially attributable to variations in genetic, lifestyle, and environmental variables. Notably, over 50% of CRC patients were identified at an advanced stage, which severely reduced the range of available treatments and deteriorated prognoses, ultimately resulting in high death rates.[3] Early detection and accurate staging are crucial for improving patient outcomes. However, current diagnostic methods often fail to provide reliable prognostic insights.[4]

Established biomarkers in CRC detection include Carcinoembryonic antigen (CEA), CD133 and epithelial membrane antigen Mucin1 (MUC1). The glycoprotein CEA has been recognized as a biomarker for colorectal cancer. Multiple organ systems, such as the digestive tract, exhibit CEA expression in both healthy fetal and adult tissues.[5] Another biomarker is CD133, which is connected with tumor development and growth processes, correlating with an increase in tumor volume and tumorigenicity.[6]

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Among the potential biomarkers mentioned in the recent studies of CRC was MUC1. MUC1 is a transmembrane glycoprotein which has gained significant attention for its aberrant expression in CRC and its association with aggressive tumor behavior. [7,8] MUC1 expression studies are also done on various malignant tumors such as ovary[9] bladder [10]and thyroid[11] tumors by various authors. A study on MUC1 expression in malignant ovarian tumors indicated that MUC1 is implicated in cancer progression and associated with poor prognosis. [9]A study on bladder cancer indicated that MUC1 is crucial in preserving the mucosal integrity of the urothelium, and its abnormal expression contributes to the growth and spread of malignant bladder tumors.[10]

In a study done on MUC1 expression in colorectal carcinoma, it was mentioned that MUC1 is indicative of poor prognosis and associated with epithelial mesenchymal transition.[12] In some studies, the correlation between MUC1 and tumor grading was observed. [13,14]

The identification and evaluation of biomarkers such as MUC1 can help to overcome the limitations of existing diagnostic approaches and improve patient care in CRC. Hence this study was undertaken to evaluate the correlation between Mucin-1 expression and grading and staging of CRC.

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AIMS AND OBJECTIVES OF THE STUDY

1. To evaluate the MUC1 expression in tumor tissue of carcinoma colon and carcinoma rectum.

2. To correlate the MUC1 expression with grading and staging of carcinoma colon and carcinoma rectum.

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REVIEW OF LITERATURE

COLORECTAL CANCER

CRC ranks third globally in terms of cancer-related deaths, and its prevalence is continuously increasing in emerging countries. Colorectal cancer frequently arises from the glandular epithelial cells of the large intestine. This occurs when particular epithelial tissue experiences genetic or epigenetic modifications that provide them with a selective advantage.[15]These hyperproliferative cells produce a benign adenoma with abnormally high survival and replication rates. Over decades, this adenoma may develop into cancer and spread of cancer. [16]Major function of the colon is to reabsorb water and the residual nutrients and minerals in the chyme. The varied microbiota in the large intestine can break down remaining proteins and carbohydrates. Crypts and villi in the lining epithelium of gastrointestinal tract enhances the absorption. Pluripotent stem cells and precursor cells present at the base of the crypt plays role in the self-renewal. [17] Pluripotent stem cells and precursor cells differentiate into various cells such as enteroendocrine cells, goblet cells, enterocytes and Paneth cells. After approximately 14 days, these cells reach the top of the villus, where apoptosis occurs and dead cells are eliminated. A gradient of signaling proteins, primarily substantially regulates this process. [17]

CRC is a diverse collection of diseases caused by a wide range of mutagens and mutations. The variety of driving mutations in colorectal cancers has hindered the development of a universal molecular treatment. [18] In instances of early detection, surgery remains the primary therapeutic option; but in approximately 25% of cases surgery becomes ineffective due to advanced stage and metastasis of CRC as seen in around 25% of cases, surgery becomes ineffective.[19] In these individuals, the swift emergence of drug resistance and cancer recurrence has hindered the effectiveness of neoadjuvant, cytotoxic treatments. [20]

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EPIDEMIOLOGY

INCIDENCE

It was mentioned in one of the reports of 2020 that lung and breast cancer are the most common malignancies worldwide followed by malignancy of colon and rectum.

Anticipated number of new cases of colorectal cancer mentioned in the report was 1,931,590. Worldwide age-standardized incidence rate (ASR) was 19.5 per lakh population per year.

Prevalence of ASR was greatest in Europe at 13.4, followed by Oceania at 29.8, North America at 26.2, Asia at 17.6, Latin America at 16.6, EMRO at 9.1, and Africa at 8.4.

The age-standardized rates for colorectal cancer were nearly four times greater in high-income populations, reaching 30.2%, compared to 8.8% in low-income populations. [21]

MORTALITY

As per the report of international agency on research CRC is the second leading cause of death related to malignancy worldwide. In 2020, there were an anticipated 935,173 fatalities, with a greater prevalence in males than in females. The highest mortality rates were noted in Europe at 12.3%, whereas the lowest were documented in Africa at 5.6% and the Eastern Mediterranean region at 5.3%. [21]

RISK FACTORS OF CRC

Effective approaches of modifiable risk factors may help in reducing risk factors of CRC and are thus particularly significant for policymakers in the development of colorectal cancer control programs.

Alcohol Consumption

Cai et al. indicated a strong correlation of alcohol intake with colorectal cancer. It was also mentioned in their study that in heavy drinkers consuming over 50 g of ethanol daily had highest risk of CRC. [22] Zou et al. indicated that alcohol consumption was causally linked to an elevated risk of colorectal cancer. They also found that alcohol may have a harmful effect via altering the expression of specific genes through DNA methylation. [23]

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Smoking

Toxic agents such as nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons, and benzene in smokers adversely affect exposed mucosal cells. Prolonged exposure of smoking can lead to molecular alterations in colorectal cells, ultimately resulting in the pro-oncogene modifications and accumulation of modified pro-oncogenes may trigger the onset of colorectal cancer. [24]

Obesity

In obesity level of cytokines such as tumor necrosis factor and interleukin-6 are high. Influence of these cytokines on proliferation of tumor cells may explains the association between obesity and the onset of colon cancer.[25]

Sedentary Lifestyle

The correlation between colorectal cancer risk and poor physical activity or a sedentary lifestyle has been documented across several groups. The findings of some study indicated that any level of physical activity can lead to 0.25 to 0.30 decrease in the risk of colorectal cancer death. [26]

Dietary factors

High intake of processed meat and high intake of fat is one of the risk factors for CRC. Cooking meat, particularly at elevated temperatures like grilling or barbecue, can generate several chemical carcinogens. Moreover, processed meat may lead to the generation of many carcinogens, such as N-nitroso compounds and polycyclic aromatic hydrocarbons. [27]

Psychological Stress

Long-term psychological stress can influence various stages of the carcinogenesis process, including instability of genomes and also leads to genetic mutation which may lead to tumor promotion. [28]

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Non-Modifiable Risk Factors.

Non-modifiable risk factors are primarily utilized to identify individuals who are at high risk. Identification of these risk factors may help in planning for prevention of CRC. Individuals over 50 years of age are particularly at elevated risk, accounting for almost 90% of all colorectal cancer cases. Various mutations in germline are the most common forms of genetically predisposed vulnerability. Commonly associated germline mutations are mutation in adenomatous polyposis coli, mutation in DNA mismatch repair gene, genes associated with familial adenomatosis polyposis and lynch syndrome. [29]

A familial history of colorectal cancer or adenomatous colonic polyps in first-degree relatives is crucial for identifying high-risk populations in colorectal cancer control programs and regimens. [30] Individuals who are exposed for radiation to abdomen and pelvic region as a part of treatment for other malignancies such as carcinoma prostate are at a high risk of gastrointestinal malignancies especially in the lower gastrointestinal tract. [31] Risk of colorectal malignancy is high in inflammatory bowel disease. The gut microbiome, referred to as "forgotten organ," also has a risk of developing malignancy in colon and rectum. [32]

ETIOPATHOGENESIS

The majority of colorectal cancers develop from precancerous polyps, which can be generally classified as serrated polyps or traditional tubular adenomas. Adenomas arise when the usual processes governing DNA repair and cellular growth are disrupted. Ongoing epithelial renewal is necessary due to the persistent loss of surface cells from the intestinal mucosa; proliferation occurs exclusively at the crypt base. As mutant cells progress towards the intestinal lumen, the normally orderly process of terminal differentiation and subsequent apoptosis is interrupted, resulting in the formation of distinct adenomas. Adenomatous polyps progressively enlarge, exhibit increasing dysplastic characteristics, and may ultimately gain invasive capability. Sequential modifications in essential growth regulating genes signify the shift from normal to hyperproliferative epithelium. This sequential advancement linking certain genetic modifications with progressive histological characteristics has established a model for solid carcinogenesis. Mutations in the

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Adenomatous polyposis coli gene (APC) which encodes a tumor suppressor, or in the B-Raf proto-oncogene, serine/threonine kinase (BRAF) oncogene, serve as initiating events that lead to the formation of conventional adenomas or serrated polyps, respectively. [33]

GRADING OF COLORECTAL CANCER

Grade 1 tumors consist of well-differentiated neoplasms exhibiting over 95% glandular development. Grade 2 tumors exhibit intermediate differentiation, characterized by 50-95% glandular development. Grade 3 tumors display weakly differentiated characteristics, consisting of fewer than 50% of glandular structures. Grade 4 tumors exhibit a lack of differentiation, characterized by the absence of glandular development and mucin synthesis.[34]

STAGING OF COLORECTAL CANCER

One of the commonly used staging system for CRC is TNM staging system which is based on the depth of invasion of the tumor in the wall of the intestine, involvement of lymph nodes and distant metastasis. Tumor staging is divided into five subgroups according to the extent invasion of tumor in the intestinal wall. When the tumor is limited to mucosa and lamina propria and invading into submucosa it is labelled as in situ carcinoma and stage Tis. When tumor invades submucosa but it is not extending beyond submucosa it is categorized as T1 stage. When tumor invades muscularis propria but not extending beyond it that stage is called as T2 stage. When the tumor invades serosa and extends to submucosa it is stage T3. In stage T4 tumor invades into adjacent structures or the visceral peritoneum. Categorization of nodal involvement is done as N0, N1 and N2. When lymph node involvement is not observed then it is categorized as N0. In N1 one to three lymph nodes are involved. When more than four lymph nodes are positive it is categorized as N2. Microscopic metastatic deposits in pericolic adipose tissue are taken as metastatic lymph nodes. When distant metastasis is absent it is categorized as M0. When distant metastasis is present it is called as M1. Spread of CRC into external or common iliac lymph nodes is categorized M1. [35]

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BIOMARKERS FOR CRC

Numerous recent studies have focused on using molecular testing to choose both conventional and targeted therapy for individuals with colorectal cancer, and this approach is quickly becoming the norm for managing CRC patients. Predictive biomarkers are molecular indicators that forecast the response to a certain medicine or treatment regimen. [33]

By binding to the extracellular domain of the Epidermal growth factor receptor (EGFR), monoclonal antibody treatments that target the EGFR disrupt EGFR signaling pathways. The primary targeted treatments for colorectal cancer have been anti-EGFR monoclonal antibodies, which depend on the mutational state of the pathway's genes as predictive biomarkers of response. Data from early clinical trials showed that anti-EGFR monoclonal antibody therapy was ineffective in treating individuals with colorectal cancer who had Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation that affected exon two codons 12 and 13. Further research revealed additional EGFR signaling pathway gene alterations affecting BRAF, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN), and other exons of KRAS and in NRAS that could impact how well CRC responds to anti EGFR antibody treatments. There are currently no clear guidelines for the molecular testing of EGFR pathway genes other than KRAS. [36]

In specific clinical scenarios, the DNA mismatch repair status of colorectal cancer may serve as a prognostic indicator. No guidelines have been published on the use of MMR as a predictive biomarker for therapeutic response, although MMR testing for colorectal cancer is recommended for all patients as part of the evaluation for probable Lynch syndrome. Microsatellite instability investigation which indicates status of mismatch repair gene, is essential for planning patients of CRC for immunotherapy, as indicated by current molecular biomarker studies. [37]

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It has been demonstrated that changes in numerous key genes involved in the formation and advancement of colorectal cancer, including defective mismatch repair gene and BRAF activating mutations, impact prognosis as indicated by several tumor progression or survival metrics. [38]

MUC1 IN CRC

MUC1 is a membranous binding mucin present on apical surface of secretory epithelial cells. The MUC1 gene contains 1201 nucleotides and is found on chromosome 1q21. Variable amounts of 20 amino-acid tandem repeats make up the N-terminal ectodomain of MUC1 which is called as MUC1-N. By attaching to pathogens it serves a protective purpose and it also has a signaling role in cells. [39]

The MUC1 N is anchored to the cell membrane as a heterodimer with MUC1-C which is a terminal subunit. The overexpression, abnormal intracellular localization, and alterations in glycosylation of this protein, observed in the majority of human carcinomas which facilitate anchorage-independent development and tumorigenicity. [40] In some studies it was mentioned that overexpression of MUC1 imparts resistance to programmed cell death triggered by oxidative stress. It also imparts resistance to anticancer drugs. [41,42]

In instances where MUC1 was expressed at the most profound invasive region of the tumor, there was a notable increase in lymphatic and venous invasion, along with metastasis. [43]

When the cytoplasmic tail of MUC1 interact with β-catenin, it significantly influences the cell cycle and cell proliferation. This process seldom occurs in typical polarized epithelium, as MUC1 is located on the apical surface, whereas β-catenin is situated on the lateral surface of epithelium. The loss of polarity during transformation facilitates the interaction between MUC1 and β-catenin. [43]

β-catenin can directly connect to the amino acid sequence within the MUC1 cytoplasmic domain. This binding is facilitated by the phosphorylation which inhibits β-catenin's binding to MUC 1 and also destroy β-catenin. Interruption of the β-catenin binding site in MUC1

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leads to inhibition of its capability to promote binding dependent and binding independent growth. It indicates that interaction of β-catenin with MUC1 is essential for its tumorigenic function. MUC1 binding with β-catenin inhibits its interaction with E-cadherin resulting in disruption of connections of cells with each other. [44] In cancer cells, MUC1 polarization is disrupted, resulting in its overexpression. Interaction between MUC1 and E-cadherin, via β-catenin binding, impairs E-cadherin-mediated cell-cell contacts at locations of MUC1 expression. This promotes proliferation and reduces cell-cell adhesion, possibly elevating carcinogenesis and metastasis. [44]

Precise mechanism of MUC1-associated carcinogenesis and proliferation of cancer cells remains poorly elucidated. MUC1 can attach to β-catenin, obstruct its nuclear translocation and inhibit the proliferation. β-catenin's association with MUC1 will inhibit its interaction with E-cadherin or Adenomatous polyposis coli gene APC. [45]

MUC1 expression in various malignant tumours

Some research indicates that the mucin family, especially MUC1, significantly contributes to the progression of lung cancer. Several lung cancer vaccines targeting MUC1 are currently in clinical trials. [46] MUC1 is expressed apically and exhibits polarity in normal tissues. MUC1 has abnormal depolarization expression and loses its polarity on the surface of cancer cells in malignant tumors, often associated with a poor prognosis. [47]

In some of the studies done on triple negative breast carcinoma it was observed that in 49 of 52 (94.2%) triple negative breast carcinoma MUC1 expression was noted. In their study based on the findings they have mentioned that MUC1 increases programmed death ligand 1 in triple negative breast carcinoma cells which may cause augmented immune evasion and also increases the invasion of the tumor cell into adjacent tissue. They also mentioned that MUC1 can be used as a possible target for inhibiting the progression of triple negative breast carcinoma.

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It can be used as a primary target for tumor immunotherapy in triple negative breast carcinoma. [48]

In some studies done on role of MUC1 expression in ovarian cancer it was mentioned that MUC1 may lead to progression of ovarian malignancies and the unfavorable prognosis of patients. They have also mentioned that MUC1 gene holds considerable promise for the clinical diagnosis and management of ovarian cancer patients. [49]

In MUC1 expression studies done in patients with cholangiocarcinoma it was mentioned that in these tumors MUC1 is upregulated hence the cancer cells are extremely invasive and prone to vascular and lymph node metastases. Hence these patients have a poor clinical prognosis. [50]

In MUC1 expression study done on gall bladder malignancy it was mentioned that MUC1 is significantly expressed in metastatic tumor cells of ascitic fluid sample of gallbladder cancer patients. [51]

In the normal urinary epithelium, MUC1 contributes to mucosal integrity and prevents urinary bacterial invasion. Aberrant expression of MUC1 in malignant bladder tumor contributes to the development and spread of bladder cancer. [10]

A study done on MUC1 expression in hepatocellular carcinoma shown that MUC1 was variably expressed in hepatocellular carcinoma with correlation of expression rate with reduced patient survival rates. They also mentioned that MUC1 may serve as a valuable therapeutic target and diagnostic marker for hepatocellular cancer. [52]

In a study done on MUC1 expression in thyroid cancer revealed that MUC1 expression was significantly elevated in papillary thyroid cancer tissues as compared to tissue of follicular carcinoma. They have mentioned that there may be variation in MUC1 expression in different thyroid cancer types. [53]

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MUC1 expression studies in CRC

Khanh et al. [12] done a study to investigate the relationship between mucin expression and other previously documented prognostic variables, such as tumor budding at invasion fronts, transforming growth factor-β1 expression, and infiltration of CD10+ myeloid cells in CRC. They have done immunohistochemical analysis of 206 colorectal samples. They arrived to the conclusion that immunosuppression and the epithelial-mesenchymal transition may be linked to poor prognoses associated with MUC1.

Imai Y et al. [54] examined mucin expression profiles in histological subtypes of colorectal cancer (CRC) in relation to clinicopathologic factors and prognosis. The researchers determined that the expression profiles of mucin core proteins and their clinical importance vary based on histological subtypes of colorectal cancer, perhaps indicating distinct pathogenic mechanisms for these cancers.

In a study done by Kesari MV et al. [13] no association was found between tumor stage or site and the expression of MUC1, MUC2, or MUC5AC. However, they observed a substantial association between MUC1 and MUC5AC expression and tumor grade.

Díaz Del Arco C et al. [14] evaluated the relationship between colorectal cancer prognosis and MUC1 expression. MUC1 expression was analyzed in 96 colorectal carcinomas using immunohistochemistry. They determined that the absence of MUC1 expression was more prevalent in cases of disease recurrence or mortality, in contrast to individuals with stable disease, who exhibited greater intensity of positive.

Singh et al. [55] assessed the immunohistochemical expression of MUC1 in different stages and differentiation of colorectal carcinoma in 35 resected specimens of colorectal carcinoma. They noted that moderately differentiated adenocarcinoma was more commonly found in their study. They concluded that there was over-expression of MUC1 in the CRC cases.

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MATERIAL AND METHODS

Study Setting: The study was carried out in Histopathology section, of Department of Pathology, BLDE (Deemed to be University), Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura.

Study Population: The study was done on resected specimens of Colorectal carcinoma sent to the Histopathology section of the Department of Pathology, from the year 2019 to the year 2024 (3 years retrospective and two years prospective).

Study Period: May 2023 to December 2024

Study Design: Hospital-based cross-sectional study.

Methods of collection of data

Resected specimens of Colorectal carcinoma sent to the Histopathology section of the Department of Pathology from 2019 to 2024 which were diagnosed as adenocarcinoma on histopathology was evaluated for grading and staging. Detailed clinical history of the patients of Colorectal carcinoma was taken for prospective cases. For retrospective cases of CRC clinical details were collected from the patient's records. Each case was evaluated under the headings of age, sex of the patient, tumour location, histological grading and staging of the tumor. Tumour tissue blocks on which diagnosis of adenocarcinoma was done was evaluated for MUC1 expression. Then correlation of MUC1 expression was done with the grading and staging of CRC.

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Immunohistochemistry (IHC) MUC1 was performed on the blocks which showed tumor tissue on the (H&E) stained slides.

1. Cut 3mm sections on charged slides and bake it at 70 degree for 20 minutes.
2. Then deparaffinization was done by two changes of xylene 10 mins each.
3. Then graded dehydration was done by absolute alcohol in 100%,70%, 50% for 3mins each. Then in distilled water 3mins each.
4. Antigen retrieval was done by keeping the sections in Tris EDTA, (pH 8.5 to 9.0).
5. Washing in distilled water for 3mins.
6. Washing in PBS/TBS buffer (Immuno wash buffer) for 3mins.
7. Three percent hydrogen peroxide was added and kept for 10 mins, followed by washing in 0.05mM Tris-buffered saline (TBS).
8. Sections were incubated with diluted mouse monoclonal antibodies against MUC1 as primary antibodies for 45mins in a moist chamber.
9. Washing was done in TBS for 2 mins.
10. Add target binder and incubate for 10mins. Wash in the TBS buffer for 2 mins.
11. Sections were incubated with Polyexcel HRP for 10mins.
12. After rinsing with TBS, they were treated with 0.5 mg/ml 3, 3'- diaminobenzidine solution for 3-5mins and wash with distilled water.
13. Counterstaining was done with haematoxylin for 30 seconds.
14. Sections were dehydrated in ethanol, cleared in xylene and then mounting of slides.
15. Appropriate positive control (known case of Mucinous adenocarcinoma breast showing score 3 MUC1 positivity) was used.

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Table 1: Evaluation of Immunohistochemistry slides was done as per the scoring mentioned in study done by Raj N et al. [56]

SCORE	STAINING PATTERN	MUC1 PROTEIN EXPRESSION
0	0% of tumour cells	Negative
1+	Less than 10% of tumour cells showing MUC1 with weak positivity	Negative
2+	10-50% of tumour cells showing MUC1 with moderate positivity	Equivocal
3+	More than 50% of tumour cells showing MUC1 with strong positivity	Positive

Sample Size:

With the Anticipated correlation between MUC1 expression of both analyzed mucin transcripts 0.602 [57] at 95% confidence level and 98 power in the study, the sample size worked out is 40.

Formula used is

N=Z+ZC2+3

The standard normal deviate for $\alpha = Z_\alpha = 1.9600$

The standard normal deviate for $\beta = Z_\beta = 2.0537$

C=0.5*ln1+r1-r=0.6963

This study requires a total sample size of 40.

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Selection Criteria:-

Inclusion criteria:

All the resected colorectal specimens diagnosed as Adenocarcinoma on histopathology was included.

Exclusion criteria:

Tissues that are inadequate for further processing for immunohistochemistry was excluded.

Statistical Method for Future Data Analysis:

- The data obtained was entered in a Microsoft Excel sheet, and statistical analysis was performed using statistical package for the social sciences (Version 20).
- Results were presented as Mean (Median)±SD, inter-quartile range, counts and percentages and diagrams.
- Categorical variables were compared using the Chi square test.
- To find the correlation between quantitative variables correlation coefficient was used. P value less than 0.05 was considered statistically significant. All statistical tests were done by two tailed tests.

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RESULTS

In the present study, 40 cases of CRC were evaluated for MUC1 expression in CRC and its correlation with grading and staging of CRC. Age of the youngest patient in the present study was 28 and oldest patient was 80 years old. Mean age of study participant was 58 ± 13.

TABLE 2: DISTRIBUTION OF THE CRC CASES BASED ON AGE GROUPS (n=40)

Age Groups	Number of cases	Percentage
21 to 30 yrs	1	2.5
31 to 40 yrs	3	7.5
41 to 50 yrs	11	27.5
51 to 60 yrs	7	17.5
61 to 70 yrs	9	22.5
71 to 80 yrs	9	22.5
Total	40	100.0

A maximum number of study participants were within the age group 41 to 50 years, amounting to 27.5%, followed by 61-70 years and 71-80 years, amounting to 22.5% cases each.

TABLE 3: GENDER AND AGE WISE DISTRIBUTION OF CRC CASES

Age Groups	Gender		Total
	Females	Males	
21 to 30 yrs	0	1	1
	0.0%	6%	2.5%
31 to 40 yrs	3	0	3
	13.0%	0.0%	7.5%
41 to 50 yrs	6	5	11
	26.1%	29.4%	27.5%
51 to 60 yrs	4	3	7
	17.4%	17.6%	17.5%
61 to 70 yrs	6	3	9
	26.1%	17.6%	22.5%
71 to 80 yrs	4	5	9
	17.4%	29.4%	22.5%
Total	23	17	40
	100.0%	100.0%	100.0%

Gender wise distribution of CRC cases showed a mild female preponderance with male to female ratio of 0.73:1.

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TABLE 4: DISTRIBUTION OF THE CRC CASES BASED ON CLINICAL PRESENTATION

Clinical Presentation	Number of cases	Percentage
Abdominal pain	4	10.0
Mass per abdomen	22	55.0
Per rectal bleeding	8	20.0
Obstructive symptoms	6	15.0

A maximum number of study participants presented with a clinical manifestation of detectable mass per abdomen, summing up to 55%, followed by per rectal bleeding (20%), obstructive symptoms (15%) and abdominal pain (10%).

TABLE 5: DISTRIBUTION OF THE CRC CASES BASED ON GROSS MORPHOLOGY

Gross morphology	Number of cases	Percentage
Circumferential	8	20.0
Exophytic	4	10.0
Polypoidal	2	5.0
Ulceroproliferative	26	65.0
Total	40	100.0

The resected specimens of the study participants showed the commonest gross presentation with ulceroproliferative growth amounting to 65%.

TABLE 6: DISTRIBUTION OF THE CRC CASES BASED ON SITE

Site	Number of cases	Percentage
Caecum	9	22.5
Colon	14	35.0
Rectum	17	42.5
Total	40	100.0

Out of the 40 cases of CRC, the commonest site involved was the rectum amounting to 42.5%, followed by the colon 35% and the caecum 22.5%.

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TABLE 7: DISTRIBUTION OF THE CRC CASES BASED ON HISTOLOGICAL TYPES

HISTOLOGICAL TYPES	Number of cases	Percentage
Mucinous adenocarcinoma	2	5
Adenocarcinoma	37	92.5
Signet ring cell carcinoma	1	2.5
Total	40	100.0

In the present study, adenocarcinoma was the predominant histological subtype, with 92.5%, followed by 5% of mucinous adenocarcinoma and 2.5% of signet ring cell carcinoma.

TABLE 8: DISTRIBUTION OF THE CRC CASES BASED ON HISTOLOGICAL GRADING

Histological grading	Number of cases	Percentage
Moderately differentiated	33	82.5
Poorly differentiated	3	7.5
Well differentiated	4	10.0
Total	40	100.0

Out of the 40 CRC cases analyzed, 82.5% of cases were moderately differentiated followed by 10% of cases well differentiated and 7.5% of cases being poorly differentiated. In poorly differentiated CRC, 2 cases were mucinous adenocarcinoma, and one case was signet ring cell carcinoma.

TABLE 9: DISTRIBUTION OF THE CRC CASES BASED ON pT STAGING

pT Staging	Number of cases	Percentage
T1	1	2.5
T2	21	52.5
T3	14	35.0
T4	4	10.0
Total	40	100.0

In the present study, a maximum number of cases were of T2 staging, amounting to 52.5%, followed by T3 (35%), T4 (10%) and T1 (2.5%).

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TABLE 10: DISTRIBUTION OF THE CRC CASES BASED ON pN STAGING

pN Staging	Number of cases	Percentage
N0	25	62.5
N1	11	27.5
N2	4	10.0
Total	40	100.0

Out of the 40 cases studied, 62.5% did not show any lymph node involvement.

In 27.5% of cases, lymph node status was N1, and in 10% of cases, N2 status was noted.

TABLE 11 – ASSOCIATION OF GRADING OF CRC WITH TUMOR STAGING

GRADING	T1	T2	T3	T4	Chi-square	p-value
Well differentiated (n=4)	0 (0.0%)	3 (75%)	1(25%)	0 (0.0%)	6.991	0.322
Moderately differentiated (n=33)	1(3.03%)	18 (54.54%)	10 (30.30%)	4 (12.13%)		
Poorly differentiated (n=3)	0 (0.0%)	0 (0.0%)	3 (100%)	0 (0.0%)		

When the association of grading was done with tumour staging, in all cases of poorly differentiated CRC, T3 staging was noted in 100% of cases, whereas in well-differentiated and moderately differentiated CRC, the association between grading and staging was 25 % and 30.30%, respectively. In poorly differentiated CRC, in 100% of cases, higher staging was observed. However, the difference was statistically not significant.

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TABLE 12 - ASSOCIATION OF GRADING OF CRC WITH LYMPH NODE METASTASIS

GRADING	N0	N1	N2	Chi-square	P value
Well differentiated (n=4)	4 (100%)	0 (0.0%)	0 (0.0%)	14.206	0.007
Moderately differentiated (n=33)	20 (60.61%)	11 (33.33%)	2 (6.06%)		
Poorly differentiated (n=3)	1 (33.33%)	0 (0.0%)	2 (66.67%)		

When the correlation between grading and lymph node metastasis was done, the highest percentage of lymph node metastasis in the N2 category was noted in poorly differentiated CRC as compared to moderate and well-differentiated CRC, and the difference was statistically significant with a p-value of 0.007.

TABLE 13- ASSOCIATION OF GRADING OF CRC WITH DEPTH OF INVASION

GRADING	DEPTH OF INVASION				Chi-square	P value
	subserosa	serosa	Muscularis propria	submucosa		
Well differentiated (n=4)	0 (0.0%)	2 (50%)	2 (50%)	0 (0.0%)	5.229	0.515
Moderately differentiated (n=33)	6 (18.19%)	8 (24.24%)	18 (54.54%)	1(3.03%)		
Poorly differentiated (n=3)	1(33.33%)	2 (66.67%)	0 (0.0%)	0 (0.0%)		
Total	**7**	12	20	1		

When the association of grading was done with depth of invasion, it was observed that in poorly differentiated CRC, the highest percentage of cases showed extension up to serosa and beyond serosa, amounting to 66.67% and 33.33%, respectively, but the difference was not statistically significant.

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TABLE 14- ASSOCIATION OF GRADING OF CRC WITH LYMPHOVASCULAR INVASION

GRADING	LYMPHOVASCULAR INVASION		Chi-square	P value
	YES	NO		
Well differentiated (n=4)	1 (25%)	3 (75%)	1.538	0.463
Moderately differentiated (n=33)	11 (33.33%)	22 (66.67%)		
Poorly differentiated (n=3)	2 (66.67%)	1 (33.33%)		

When correlation of lymphovascular invasion was done with grading, it was observed that in poorly differentiated CRC, the highest number of cases showed lymphovascular invasion, amounting to 66.67%, followed by moderately differentiated CRC, amounting to 33.33%. In well differentiated CRC cases, 25% showed lymphovascular invasion. However, the difference is not statistically significant.

TABLE 15 - ASSOCIATION OF STAGING OF CRC WITH LYMPH NODE METASTASIS

STAGING	N0	N1	N2	Chi-square	p-value
T1 (n=01)	1 (100%)	0(0.0%)	0(0.0%)	3.55	0.73
T2 (n=21)	16(76.19%)	4(19.04%)	1(4.76%)		
T3 (n= 14)	7(50%)	5(35.71%)	2(14.28%)		
T4 (n= 4)	1(25%)	2(50%)	1(25%)		

When the association of lymph node metastasis was done with the staging of CRC, the highest association of lymph node metastasis was noted in stage T4, amounting to 25%, followed by stage T3 and T2. However, the difference was not statistically significant. In all cases of the T1 stage, no lymph node metastasis was noted.

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TABLE 16 - ASSOCIATION OF STAGING OF CRC WITH DEPTH OF INVASION

STAGING	subserosa	serosa	Muscularis propria	submucosa	Chi square	p value
T1(n=1)	0(0.0%)	0(0.0%)	0(0.0%)	1 (100%)	20.85	0.013
T2 (n=21)	2(9.52%)	3(14.29%)	16(76.19%)	0(0.0%)		
T3 (n=14)	5(35.71%)	6(42.86%)	3(21.43%)	0(0.0%)		
T4 (n= 4)	0(0.0%)	3(75%)	1 (25%)	0(0.0%)		

When the association between staging and depth of invasion was studied, in stage T3 and stage T4, the highest number of cases showed the depth of invasion into serosa and subserosa, and the difference was statistically significant.

TABLE 17 - ASSOCIATION OF STAGING OF CRC WITH LYMPHOVASCULAR INVASION

STAGING	LYMPHOVASCULAR INVASION		Chi-square	p-value
	YES (n=14)	NO (n=26)		
T1 (n=1)	0(0.0%)	1 (100%)	1.63	0.65
T2 (n=21)	6(28.57%)	15(71.43%)		
T3 (n=14)	5(35.71%)	9(64.29%)		
T4 (n= 4)	3(75%)	1(25%)		

The correlation of staging with lymphovascular invasion showed maximum number of cases of T4 stage were showing lymphovascular invasion amounting to 75%, but the difference was statistically not significant.

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TABLE 18: DISTRIBUTION OF THE CRC CASES BASED ON SCORING OF MUC1

Scoring of MUCI	Number of cases	Percentage
1.0	3	7.5
2.0	9	22.5
3.0	28	70.0
Total	40	100.0

Out of the 40 cases, MUC1 expression showed a score of 3 in 28 cases (70%), followed by a score of 2 in 9 cases (22.5%) and a score of 1 in 3 cases (7.5%). In 70% of cases of CRC score 3, MUC1 expression was noted.

TABLE 19- ASSOCIATION OF GRADING OF CRC AND MUC1 EXPRESSION

Grading	SCORE 1	SCORE 2	SCORE 3	Chi-square	p-value
Well differentiated (n=4)	1 (25%)	1 (25%)	2 (50%)	3.29	0.51
Moderately differentiated (n=33)	2 (6.06%)	8 (24.24%)	23 (69.70%)		
Poorly differentiated (n=3)	0 (0.0%)	0 (0.0%)	3 (100%)		

When the association of grading and a score of MUC1 expression in CRC was done, the highest number of poorly differentiated CRC cases showed score 3 MUC1 expression, followed by moderately differentiated CRC cases amounting to 100% and 69.70%, respectively, but the difference was not statistically significant.

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TABLE 20: ASSOCIATION OF TUMOR STAGING OF CRC AND MUC1 EXPRESSION

TUMOR STAGING	SCORE 1	SCORE 2	SCORE 3	Chi-square	p-value
T1 (n=1)	1 (100%)	0 (0.0%)	0 (0.0%)	13.81	0.032
T2(n=21)	1 (4.76%)	6 (28.57%)	14 (66.67%)		
T3 (n=14)	1 (7.14%)	2(14.29%)	11 (78.57%)		
T4 (n=4)	0 (0.0%)	1(25%)	3 (75%)		

Correlation of tumor staging with MUC1 expression showed a maximum number of cases showing score 3 expression in stage T3 and T4 amounting to 78.57% and 75% respectively.

All cases of stage T1 showed score 1 MUC1 expression and the difference between various tumor staging with MUC1 expression score was statistically significant.

TABLE 21: ASSOCIATION OF LYMPH NODE METASTASIS OF CRC AND MUC1 EXPRESSION

LYMPH NODE METASTASIS	SCORE 1	SCORE 2	SCORE 3	Chi-square	P value
N0 (n=25)	3 (12%)	7 (28%)	15 (60%)	4.218	0.377
N1 (n=11)	0 (0.0%)	2 (18.18%)	9 (81.82%)		
N2 (n=4)	0 (0.0%)	0 (0.0%)	4 (100%)		

Score 3 MUC1 expression was highest in CRC cases of lymph node metastasis in the N2 category, amounting to 100%, and lowest in the N0 category, amounting to 60%. However, the difference was statistically not significant.

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TABLE 22: ASSOCIATION OF DEPTH OF INVASION AND MUC1 EXPRESSION

DEPTH OF INVASION	SCORE 1	SCORE 2	SCORE 3	Chi-square	P value
Subserosa (n=7)	0 (0.0%)	1 (14.29%)	6 (85.71%)	13.601	0.034
Serosa (n=12)	1 (8.33%)	3 (25%)	8 (66.67%)		
Muscularis propria (n=20)	1 (5%)	5 (25%)	14 (70%)		
Submucosa (n=1)	1 (100%)	0 (0.0%)	0 (0.0%)		

When the association of depth of invasion and MUC1 expression was done, a maximum number of cases showing the depth of invasion in subserosa showed the highest score that is Score 3, amounting to 85.71% and Score 3 MUC1 expression was not observed in cases of CRC limited to submucosa and difference between depth of invasion into various layers and MUC1 expression score was statistically significant.

TABLE 23: ASSOCIATION OF LYMPHOVASCULAR INVASION AND MUC1 EXPRESSION

LYMPHOVASCULAR INVASION	SCORE 1	SCORE 2	SCORE 3	Chi-square	p value
YES (n=14)	1(7.14%)	2(14.29%)	11(78.57%)	0.876	0.645
NO (n=26)	2(7.70%)	7(26.92%)	17(65.38%)		

When the association of lymphovascular invasion and MUC1 expression was done, score 3 MUC1 expression was noted in more cases showing lymphovascular invasion as compared to CRC cases without lymphovascular invasion, but the difference was not statistically significant.

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TABLE 24- ASSOCIATION OF SITE OF CRC AND MUC1 EXPRESSION

SITE	SCORE 1	SCORE 2	SCORE 3	Chi-square	P value
Caecum (n=9)	1 (11.11%)	0 (0.0%)	8(88.89%)	4.26	0.37
Colon (n=14)	2(14.29%)	2 (14.29%)	10(71.42%)		
Rectum (n=17)	0 (0.0%)	7 (41.18%)	10(58.82%)		

Score 3 expression of MUC1 was noted in more cases of CRC of the caecum, followed by the colon and rectum. However, the difference was not significant statistically.

TABLE 25- ASSOCIATION OF GROSS MORPHOLOGY OF CRC AND MUC1 EXPRESSION

GROSS MORPHOLOGY	SCORE 1	SCORE 2	SCORE 3	Chi-square	P value
Circumferential (n=8)	0 (0.0%)	3 (37.5%)	5(62.5%)	1.59	0.95
Exophytic (n=4)	1(25%)	1(25%)	2(50%)		
Polypoidal (n=2)	0 (0.0%)	0 (0.0%)	2(100%)		
Ulceroproliferative (n=26)	2(7.70%)	5(19.23%)	19(73.07%)		

When the association of gross morphology in CRC and MUC1 expression was done, Score 3 expression of MUC1 was highest in CRC cases presenting with polypoidal growth followed by ulceroproliferative growth and circumferential growth, but the difference was statistically not significant.

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TABLE 26- ASSOCIATION OF HISTOLOGICAL TUMOR TYPES OF CRC AND MUC1 EXPRESSION

HISTOLOGICAL TUMOR TYPES	SCORE 1	SCORE 2	SCORE 3	Chi square	P value
Mucinous Adenocarcinoma (n=2)	0 (0.0%)	0 (0.0%)	2(100%)	3.66	0.45
Adenocarcinoma (n=37)	3(8.11%)	9 (24.32%)	25 (67.57%)		
Signet ring cell carcinoma (n=1)	0 (0.0%)	0 (0.0%)	1(100%)		

Score 3 MUC1 expression was noted in all cases of signet ring cell carcinoma and mucinous adenocarcinoma amounting to 100 %, however the difference was statistically not significant.

TABLE 27- ASSOCIATION OF AGE IN CRC AND MUC1 EXPRESSION

AGE	SCORE 1	SCORE 2	SCORE 3	Chi square	P value
21 to 30 yrs (n=1)	0 (0.0%)	0 (0.0%)	1(100%)	5.62	0.84
31 to 40 yrs (n=3)	0 (0.0%)	2(66.67%)	1(33.33%)		
41 to 50 yrs (n=11)	2 (18.18%)	2 (18.18%)	7 (63.64%)		
51 to 60 yrs (n=7)	0 (0.0%)	1(14.29%)	6(85.71%)		
61 to 70 yrs (n=9)	0 (0.0%)	1(11.11%)	8(88.89%)		
71 to 80 yrs (n=9)	1(11.11%)	3 (33.33%)	5(55.56%)		

There was no positive association between the age of patients of CRC and MUC1 expression.

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TABLE 28- ASSOCIATION OF GENDER OF CRC AND MUC1 EXPRESSION

GENDER	SCORE 1	SCORE 2	SCORE 3	Chi square	P value
MALES (n=17)	1 (5.88%)	3 (17.65%)	13 (76.47%)	0.17	0.91
FEMALES (n=23)	2 (8.70%)	6 (26.09%)	15 (65.22%)		

Score 3 MUC1 expression was slightly higher in males as compared to females, however the difference was statistically not significant.

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PHOTOGRAPHS/IMAGES

FIGURE 1- Photomicrograph showing gross morphology of CRC in proximal part of rectum.

FIGURE 2- Cut section- ulceroproliferative growth noted.

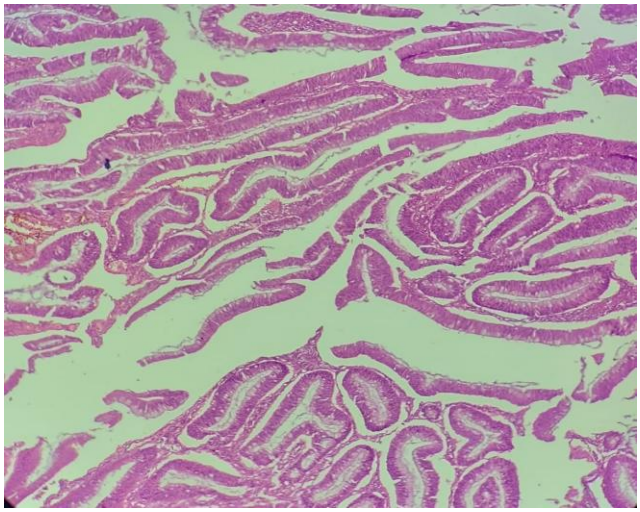

FIGURE 3- Photomicrograph showing Well Differentiated Adenocarcinoma- Rectum (H&E-100X)

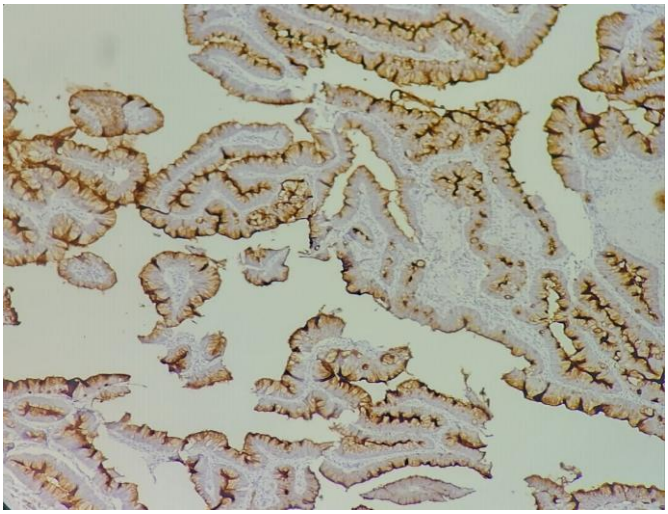

FIGURE 4- Photomicrograph showing Well Differentiated Adenocarcinoma with Score 3 MUC1 expression (IHC-100X)

Docusign Envelope ID: E765E91B-DA74-4293-8A75-AFED403BC0D1

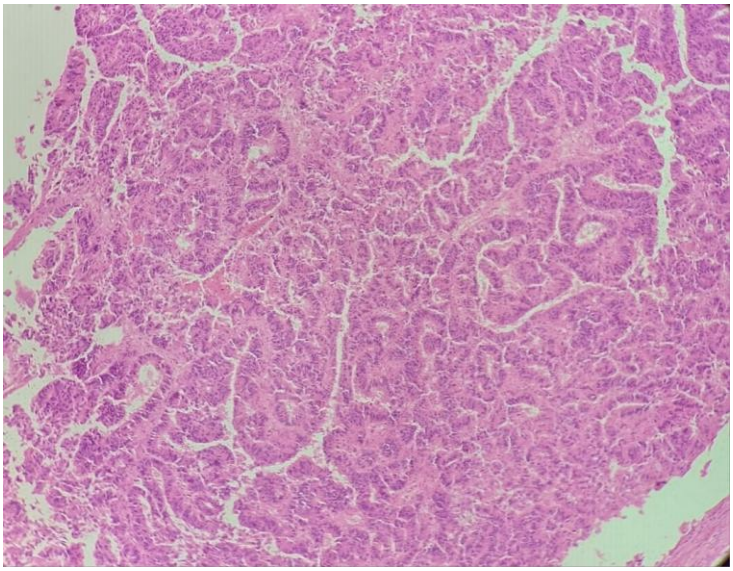

FIGURE 5- Photomicrograph showing Well Differentiated Adenocarcinoma (H&E- 100X)

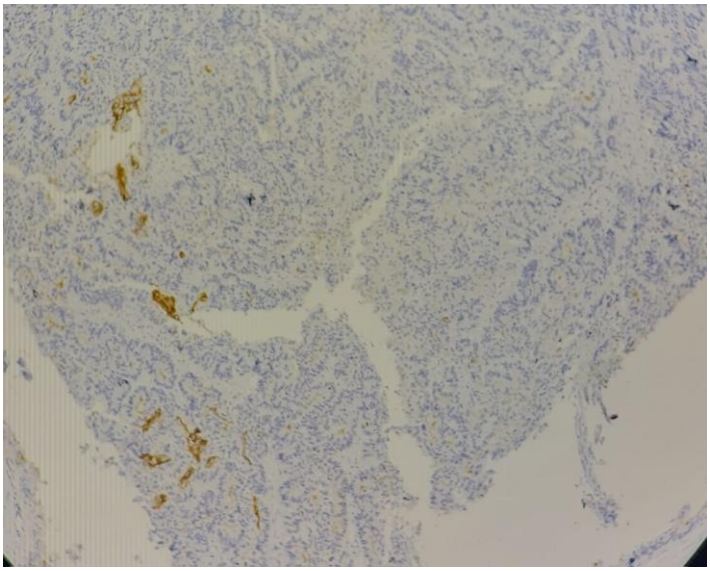

FIGURE 6- Photomicrograph showing Well Differentiated Adenocarcinoma with Score 1 MUC1 expression (IHC-100X)

FIGURE 7- Photomicrograph showing gross morphology of CRC in the transverse colon

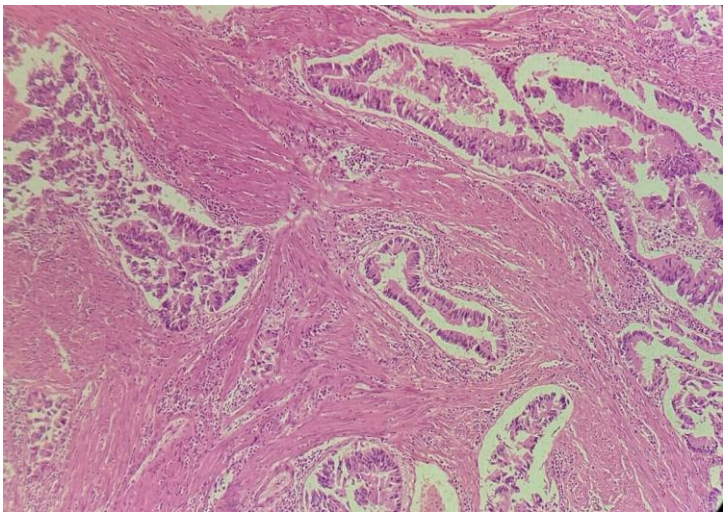

FIGURE 8- Photomicrograph showing Moderately Differentiated adenocarcinoma (H&E-100X)

Docusign Envelope ID: E765E91B-DA74-4293-8A75-AFED403BC0D1

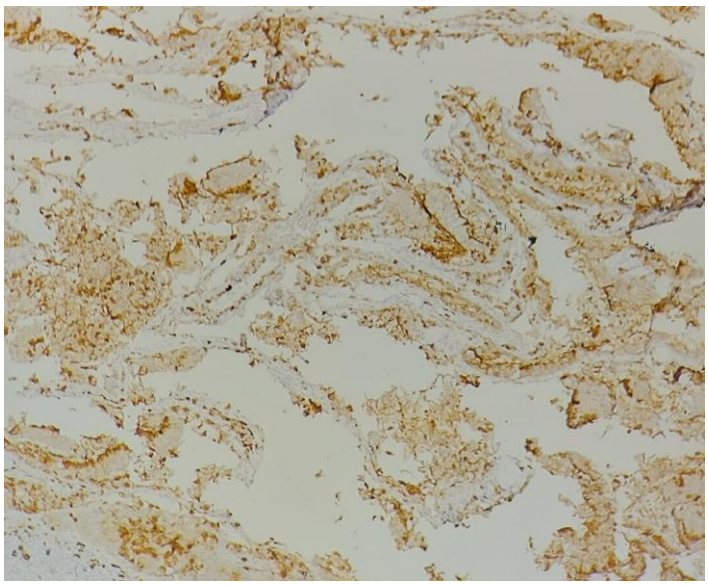

FIGURE 9- Photomicrograph showing Moderately Differentiated Adenocarcinoma with Score 3 MUC1 expression (IHC-100X)

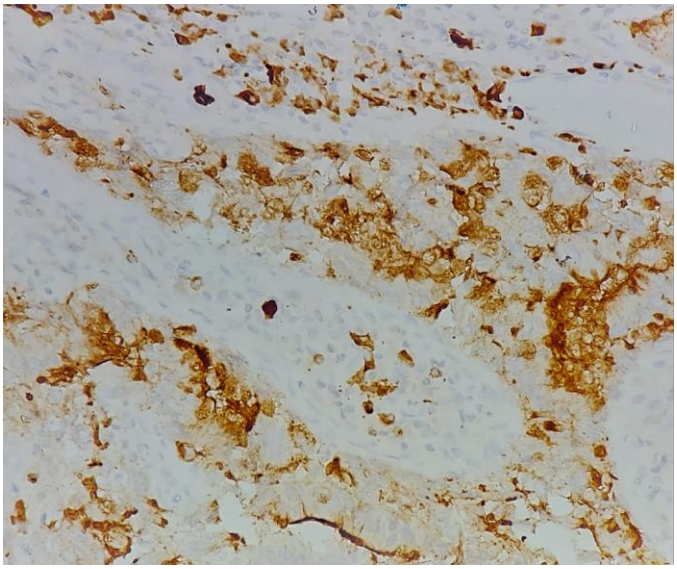

FIGURE 10- Photomicrograph showing Moderately Differentiated Adenocarcinoma with Score 3 MUC1 expression (IHC-400X)

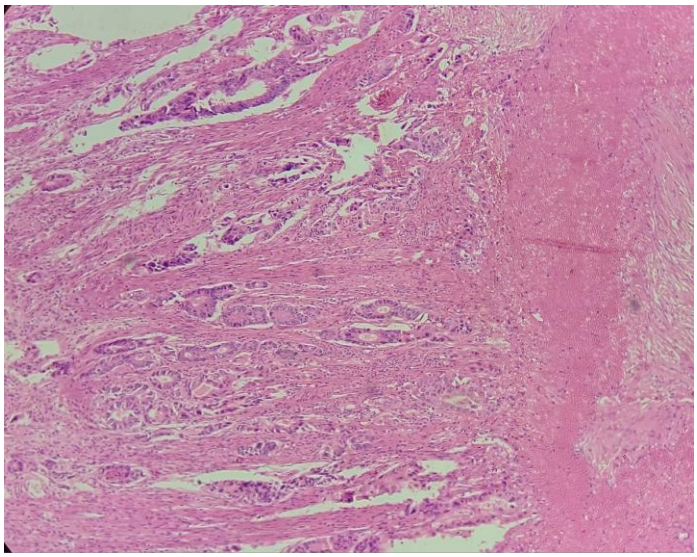

FIGURE 11- Photomicrograph showing Moderately differentiated Adenocarcinoma (H&E-100X)

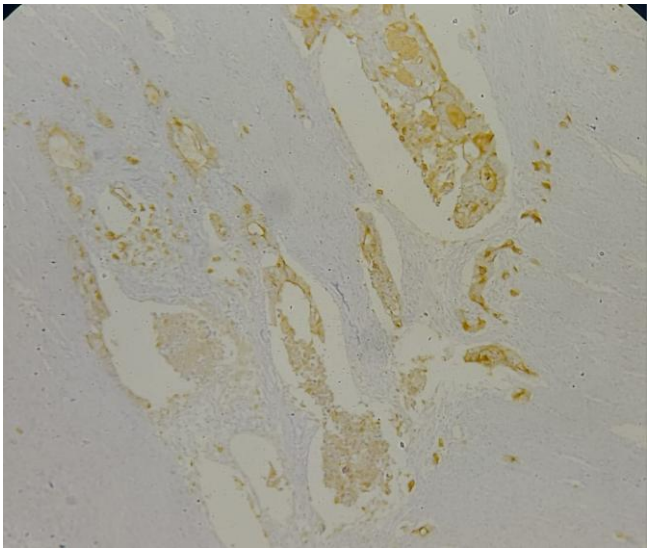

FIGURE 12- Photomicrograph showing Moderately differentiated adenocarcinoma with Score 2 MUC1 expression (IHC-100X)

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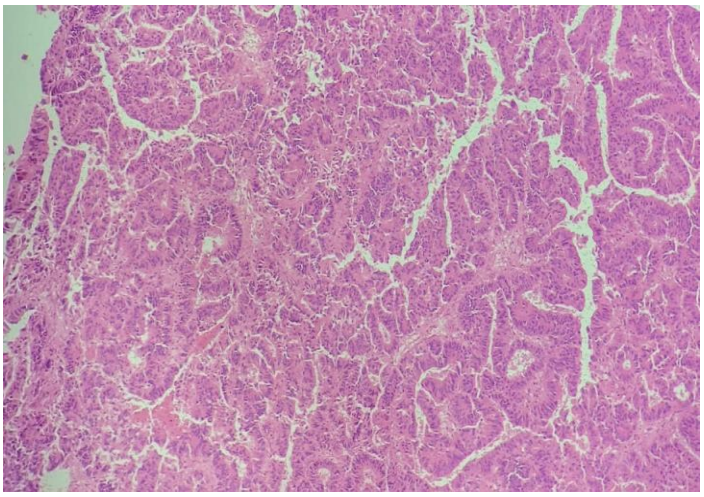

FIGURE 13- Photomicrograph showing Moderately Differentiated Adenocarcinoma (H&E- 100X)

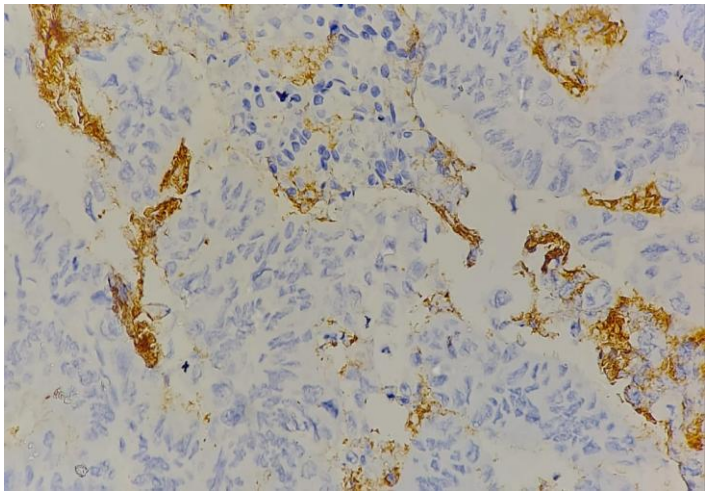

FIGURE 14- Photomicrograph showing Moderately Differentiated Adenocarcinoma with Score 1 MUC1 expression (IHC-100X)

FIGURE 15- Photomicrograph showing gross morphology of CRC in the hepatic flexure of colon

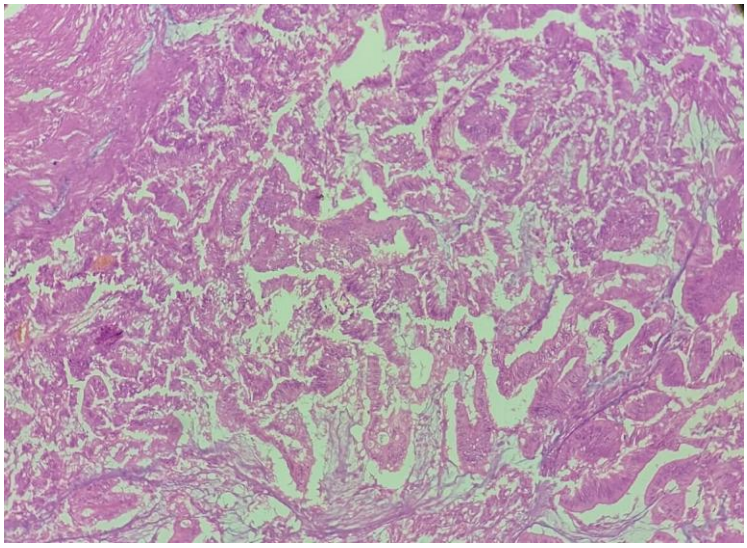

FIGURE 16- Photomicrograph showing Moderately Differentiated Adenocarcinoma (H&E- 100X)

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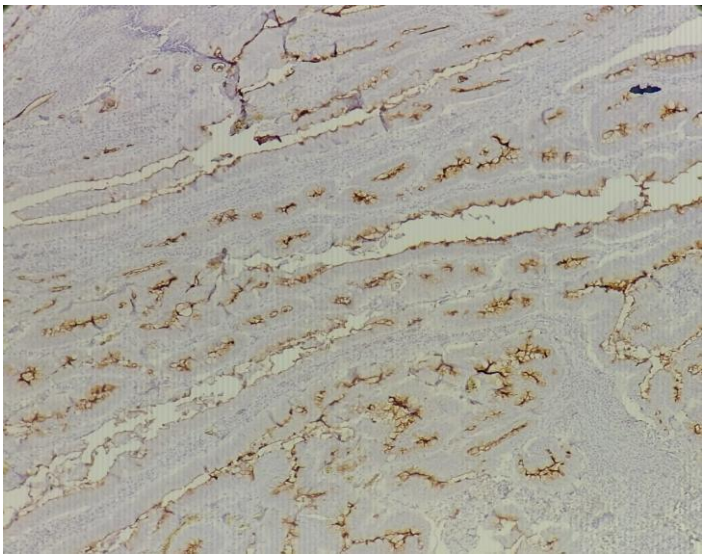

FIGURE 17- Photomicrograph showing Moderately differentiated Adenocarcinoma with Score 3 MUC1 expression (IHC- 100X)

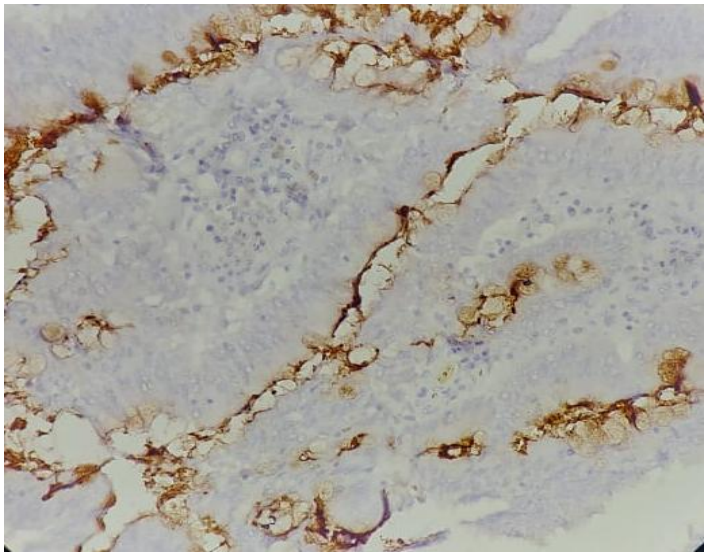

FIGURE 18- Photomicrograph showing Moderately differentiated Adenocarcinoma with Score 3 MUC1 expression (IHC- 400X)

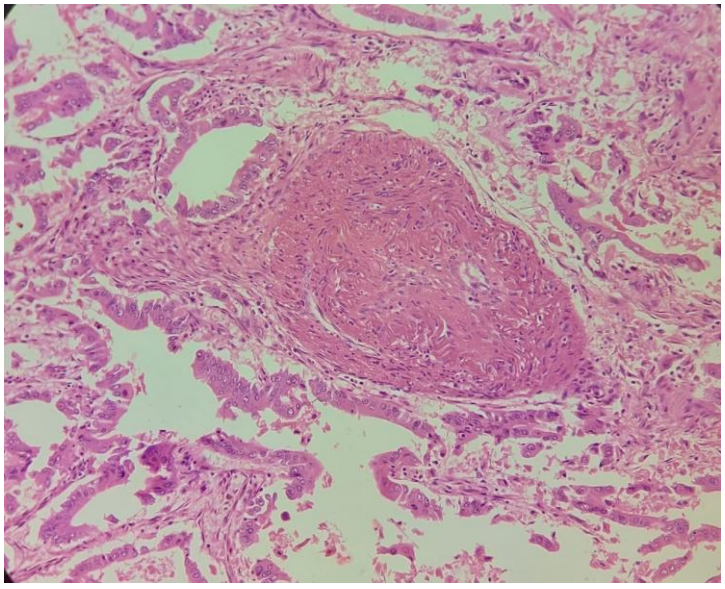

FIGURE 19- Photomicrograph showing Moderately differentiated Adenocarcinoma with perineural invasion (H&E- 200X)

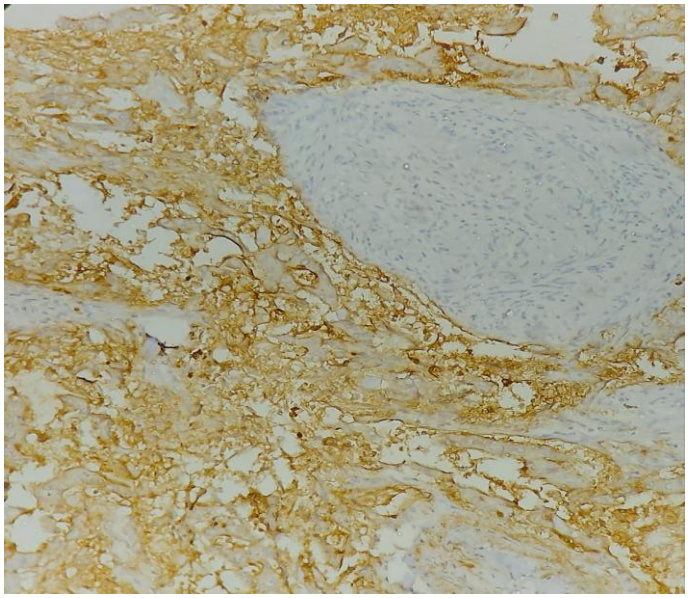

FIGURE 20- Photomicrograph showing Score 3 MUC1 expression with perineural invasion (IHC-200X)

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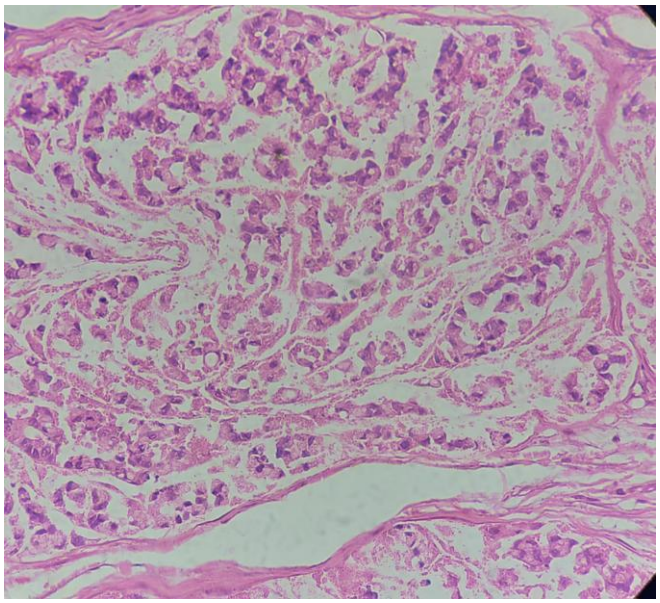

FIGURE 21- Photomicrograph showing high power view of poorly differentiated – Signet ring cell carcinoma (H&E-400X)

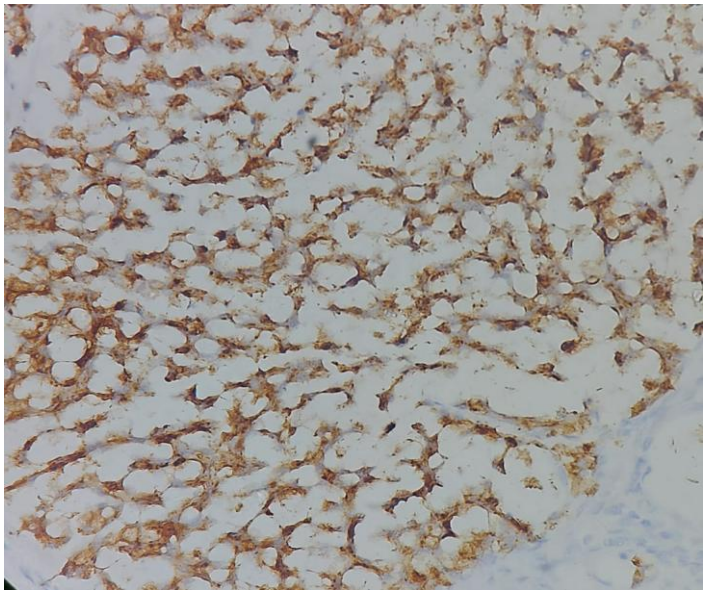

FIGURE 22- Photomicrograph showing Score 3 MUC1 expression in poorly differentiated – Signet ring cell carcinoma expression (IHC-400X)

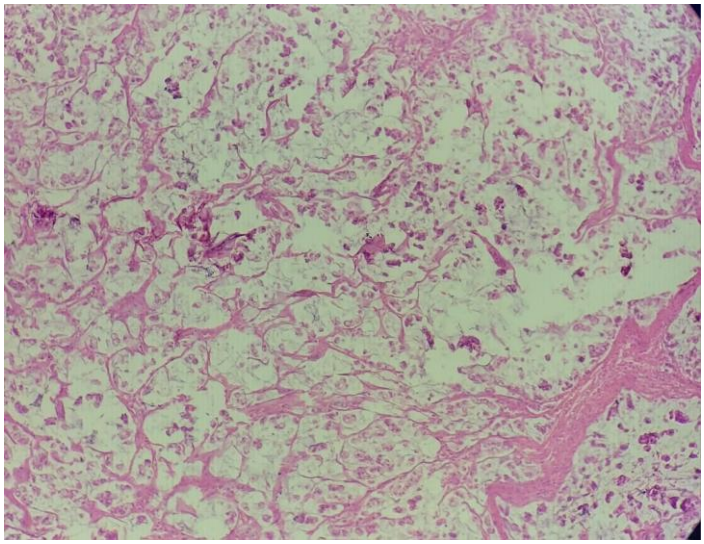

FIGURE 23- Photomicrograph showing Mucinous Adenocarcinoma – Rectum (H&E-100X)

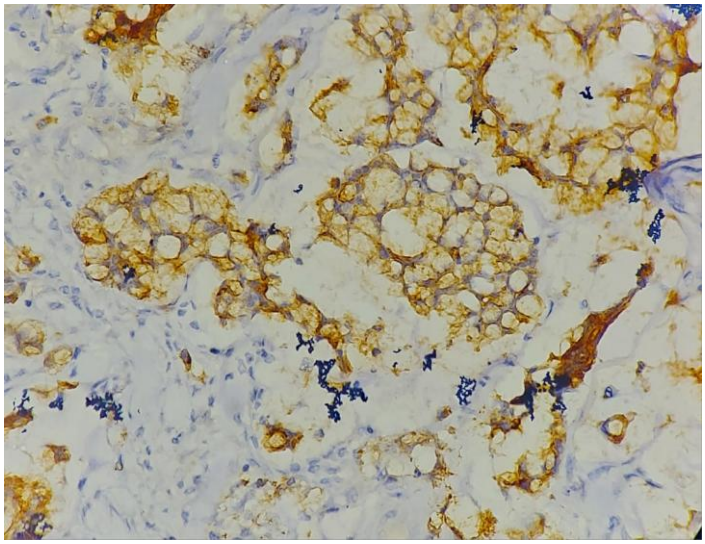

FIGURE 24- Photomicrograph showing Score 3 MUC1 expression in Mucinous Adenocarcinoma- Rectum (IHC-400X)

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DISCUSSION

In the TNM staging system for colorectal carcinoma, it was mentioned that T (tumor depth) and N is lymph node metastasis, and M stands for distant metastasis. Invasion of tumor and lymph node involvement depends on the expression of specific molecules within the tumor cells. [58] A distinguishing feature of colorectal carcinoma is their capacity to secretion of mucin. Usually, the mucin protects epithelial surfaces by lubricating the surface of the epithelium. The composition of mucin differs with the position and other pathophysiologic situations. Mucins are the most abundant macromolecules in mucus and are responsible for its biochemical and biophysical properties. [13]

The mean age of CRC in the present study was 58 ± 13 years with maximum number of study participants within the age group 41 to 50 years. These findings are in concordance with the findings of Kesari et. al, [13] and Debbarma B et. al, [55] who also observed the mean age of presentation of 55 years and 56.1 ± 15.8 years.

In various studies, it was observed that the incidence of CRC was slightly higher in males as compared to females. In these studies, it was mentioned that sex steroid hormones and microbiota of the gastrointestinal tract. [13] In a study done by Khanh DT et. al [12] and Imai Y et. al [54] male preponderance was noted amounting to 55.3% and 61.9%. Kesari et. al [13] also noted that 60% of patients were males. On the contrary, in the present study, mild female preponderance was noted amounting to 42.5% males and 57.5% females.

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The clinical symptoms of tumors vary across different anatomical regions in the colon and rectum, due to their distinct anatomical and physiological functions. Typically, abdominal pain and systemic symptoms are prevalent in right colon cancer, while hematochezia and obstruction are more frequent in left colon cancer, and alterations in defecation habits are more characteristic of rectal cancer. [59] In the present study, maximum number of study participants presented with a detectable mass per abdomen, summing up to 55%, followed by per rectal bleeding (20%), obstructive symptoms (15%) and abdominal pain (10%). Kesari et.al [(13)]noted that the most common clinical complaints were blood in stool in 66%, pain in the abdomen and mass per abdomen in 48 % of cases, and changed bowel habits in 43 %.

In the resected specimens of the CRC cases, the commonest gross presentation was ulceroproliferative growth, amounting to 65% in the present study. In other author studies ulceroproliferative growth was noted in 48 % of cases of CRC. [13]In a study done by Ahmed Khan et. al, [60] it was found that the most commonly seen gross presentation was ulcerative, 37.8% followed by 33.7% infiltrative and 23.7% proliferative.

In the present study, out of the 40 cases of CRC, commonest site involved was rectum amounting to 42.5% followed by the colon, 35% and caecum, 22.5%. In the same way, Kesari et. al [13]found that CRC most often happened in the rectum and ascending colon amounting to 30 % each. This was followed by the sigmoid colon in 26 %, and the descending colon in 8 % and in the transverse colon ,6 % of cases. Díaz del Arco C et.al [14] noted that 60.4% of tumors were located in the rectum, 21.9% in the sigmoid colon, 9.4% in the ascending colon, 3.1% in the transverse colon and 2.1% in the descending colon.

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In the present study, adenocarcinoma was the predominant histological subtype, with 92.5% followed by 5% of mucinous adenocarcinoma and 2.5% of signet ring cell carcinoma. Similar observations were noted in a study done by Debbarma B et. al [55]and Duncan TJ et. al [61] which showed that adenocarcinoma was the predominant histological subtype.

In the present study, out of the 40 CRC cases analysed, 82.5% of cases were moderately differentiated followed by 10% of cases that were well differentiated and 7.5% of cases that were poorly differentiated. Similarly, Debbarma B et. al [55] also noted that majority of the tumors were of moderately differentiated followed by poorly differentiated.

pT staging

In the present study, a maximum number of cases were of pT stage T2 amounting to 52.5% followed by T3 (35%), T4 (10%) and T1 (2.5%). Similarly, in a study by Kesari et. al, [13] 46% of cases were in stage pT2, followed by the pT3 stage in 44 % of cases, pT stage 1 in 6 % of cases, and stage 4 in 4 % of cases of CRC. These findings are similar to the findings of the present study, with a maximum number of cases in the pT2 stage. On the contrary, Díaz del Arco C et. al [14] noted that 60.3% of tumors were T3, 16.6% were T2, 8.3% were T1, 8.3% were Tis and 6.2% were T4.

pN staging

In the present study, out of the 40 cases studied, 62.5% did not show any lymph node involvement followed by N1 cases amounting to 27.5%, followed by N2 cases (10%). On the contrary, Díaz del Arco C et. al [14] noted that lymph node metastases in 39.6% of the cases with N1 status in 22.1% cases and N2 status in 14.8%.

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GRADING WITH LYMPH NODE METASTASIS

In the present study, four patients with well differentiated CRC showed N0 lymph node involvement. Out of 33 patients with moderately differentiated CRC, 20 (60.6%) showed N0 lymph node involvement, 11 (33.3%) showed N1 lymph node involvement and two patients (6.06%) showed N2 involvement. Out of 3 patients with poorly differentiated CRC, one case (33.3%) showed N0 lymph node involvement and two patients (66.6%) showed N2 involvement. The difference between grading and lymph node metastasis was statistically significant with p value 0.007. In a study done by Kristoffer Derwinger et.al, [62] on 1239 patients who underwent surgical resection for colorectal cancer, demonstrated a substantial correlation between that tumor grading and tumor staging, as well as the risk of lymph node metastasis ($p < 0.0001$). The higher grade correlated with an increased positive lymph node count in stage III illness ($p < 0.0002$).

STAGING WITH DEPTH OF INVASION

Depth of submucosal invasion is considered as an important predictive factor for lymph node metastasis. In the present study, one patient with T1 stage had submucosal involvement. Out of 21 patients with stage T2, subserosal involvement was seen in two patients (9.52%), three patients (14.28%) showed involvement of serosa, and 16 patients (76.19%) showed muscularis propria involvement. Out of 14 patients with stage T3, subserosal involvement was seen in five patients (35.71%), six patients (42.85%) showed serosa involvement and three patients (21.42%) showed muscularis propria involvement. Out of 4 patients with T4 stage CRC, 3 patients (75%) showed serosa involvement and one patient (100%) showed muscularis propria involvement. The association of staging with depth of invasion was statistically significant. ($p=0.013$). Sebastian Foersch et.al, [63] pT3b observed that tumors with an infiltration depth of more than 3 mm showed a worse prognosis when compared to pT3a tumours in which invasion of tumor tissue in the adipose tissue was 3 mm or less.

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ASSOCIATION OF TUMOR STAGING, GRADING, LYMPH NODE METASTASIS, DEPTH OF INVASION, AND LYMPHOVASCULAR INVASION WITH MUC1 EXPRESSION

In the present study, the association of tumor staging of CRC and MUC1 expression showed more cases of CRC, showing T3 and T4 stages, and MUC1 showed a statistically significant difference with a p-value of 0.03. Similar observations were noted in a study done by Yu et. al. They also observed a statistically significant correlation of MUC1 positivity with Dukes staging of CRC. [64]

In the present study, association of grading with MUC1 expression showed score 3 MUC1 expression in all cases of poorly differentiated adenocarcinoma, but the difference was statistically insignificant. These observations were similar to Khemeri et. al [65] studies which showed that on comparing low grade (G1) with high grade G2/G3 tumors, the high grade-tumors showed significantly stronger MUC1 expression. An increase in MUC1 intensity was noticed in undifferentiated tumor cells which is similar to the study findings of Kesari MV et. al [13] and Yu XW et al. [64]

In the present study**,** when association of lymph node metastasis with MUC1 expression was done highest number of CRC cases, with N2 and N1 showed higher percentage of CRC with a score 3 MUC1 expression. However, the difference was statistically not significant. A study by Aisawa et. al [66] revealed that 38.8% of MUC1-positive colorectal tumors demonstrated lymph node metastasis in contrast to MUC1-negative tumors; these findings were statistically significant. The observation suggested a higher quantity of lymph node metastases in MUC1-positive cases suggests that MUC1-mediated pathways may promote the migration of carcinoma cells to lymph nodes through stromal lymphatic channels. [66] Similar explanation may hold true in the present study also.

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In the present study, there was positive association between depth of invasion and MUC1 expression with a statistically significant difference with a p value of 0.03. Similarly in a study done by Aisawa et. al[66], 26 cases showed positive MUC1 expression, among which highest number of cases showed depth of invasion beyond serosa and the difference was statistically significant.

The association between lymphovascular invasion and MUC1 expression was not significant in the present study. Similarly, in a study done by Betge et.al [67] 13% of cases with high MUC1 expression showed lymphovascular invasion, and 56% of cases with low MUC1 expression showed lymphovascular invasion, however the difference was not statistically significant.

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SUMMARY

- This was a hospital-based cross-sectional study done on resected specimens of colorectal carcinoma sent to the histopathology section of the Department of Pathology between 2019-2024 to evaluate the MUC1 expression in tumor tissue of carcinoma colon and carcinoma rectum.
- The mean age of CRC in the present study was 58 ± 13 years, with mild female preponderance.
- Majority of the patients of CRC were presented with complaints of mass per abdomen amounting to 55%, followed by per rectal bleeding (20%), obstructive symptoms (15%) and abdominal pain (10%).
- The resected specimens of the study participants showed the commonest gross presentation of ulceroproliferative growth, amounting to 65%.
- Out of the 40 cases of CRC, the commonest site involved was the rectum amounting to 42.5%, followed by the colon 35% and the caecum 22.5%.
- Moderately differentiated adenocarcinoma was the predominant histological subtype of CRC. amounting to 82.5% of cases, followed by 10% of cases well differentiated and 7.5% of cases were poorly differentiated.
- The correlation between grading and lymph node metastasis showed the highest percentage of lymph node metastasis in the N2 category was noted in poorly differentiated CRC as compared to moderate and well-differentiated CRC. The correlation was significant statistically, with a p-value of 0.007.
- Maximum number of cases were of T2 staging amounting to 52.5% followed by T3 (35%), T4 (10%) and T1 (2.5%). When the association between staging and depth of invasion was studied, in stage T3 and stage T4, the highest number of cases showed the depth of invasion into serosa and subserosa, and the difference was statistically significant.

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- When the association of depth of invasion and tumour staging was done with MUC1 expression, score 3 MUC1 expression was more in cases of CRC, showing the depth of invasion into serosa and subserosa and stage 3 and stage 4 CRC, and the difference was statistically significant.
- When the association of grading, lymph node metastasis, and lymphovascular invasion with MUC1 expression was done, more cases of CRC showing high-grade CRC, lymph node metastasis and lymphovascular invasion showed MUC1 expression of score 3. However, the difference was statistically not significant.

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CONCLUSION

High MUC1 expression, that is, score 3 expressions, was noted in CRC cases showing high stage of CRC and CRC cases showing the depth of invasion beyond serosa and subserosa with a significant statistical difference. Also, score 3 MUC1 expression was more in cases of CRC showing poorly differentiated CRC, CRC cases with lymph node metastasis and lymphovascular invasion, but the difference was not significant statistically. This may be due to the small sample size of cases of poorly differentiated CRC cases and CRC cases showing lymph node metastasis. These findings suggest that a high score of MUC1 leads to interruption of cell adhesion leading to metastasis and invasion. Based on this, we conclude that MUC1 expression may be upregulated in colorectal carcinoma. This effect of MUC1 may play a role in the progression of tumor and the aggressiveness of CRC. However, further multicentric studies are needed with a greater number of samples to validate the study observation.

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ANNEXURE-I

ETHICAL CLEARANCE

Azadi Ka Amrit Mahotsav

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 932/2023-24 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinized the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "EVALUATION OF MUCIN 1 EXPRESSION AND ITS CORRELATION WITH GRADING & STAGING IN COLORECTAL CARCINOMA".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR. KEZIA ANNA JACOB

NAME OF THE GUIDE: DR.SUREKHA U. ARAKERI, PROFESSOR AND HEAD, DEPT. OF PATHOLOGY.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, In
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail:office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

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ANNEXURE- II

B.L.D.E (Deemed to be University) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL &RESEARCH CENTER, VIJAYAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____, S/O D/O W/O_____,

aged_____years, ordinarily resident of_____do hereby state/declare that

Dr KEZIA ANNA JACOB of SHRI BM PATIL MEDICAL COLLEGE Hospital has examined me thoroughly on___at___(place) and it has been explained to me in my own language that I am suffering from ____disease (condition) and this disease/condition mimic following diseases.

Further Doctor informed me that he/she is conducting dissertation/research titled "EVALUATION OF MUCIN 1 EXPRESSION AND ITS CORRELATION WITH GRADING AND STAGING OF COLORECTAL CARCINOMA" under the guidance of Dr. SUREKHA U. ARAKERI requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post- operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure adverse result may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study will help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also, I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

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The Doctor has also informed me that information given by me, observation made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time, I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient: Signature of doctor:

Witness: 1.

2.

Date:

Place

Docusign Envelope ID: E765E91B-DA74-4293-8A75-AFED403BC0D1

B.L.D.E (DEEMED TO BE UNIVERSITY)
ಶ್ರೀ ಬಿ.ಎಂ.ಪಟ್ಟೀಲ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ವಿಜಯಪುರ
586103
ಪ್ರಬಂಧ/ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಮಾಹಿತಿ ಪಡೆದ ಸಮ್ಮತಿ

ನಾನು, ಕೆಳಗಿನವರು_____ ಸಹಿಯಿಟ್ಟವರು, ಮಗ/ಮಗಳು/ಪತ್ನಿಯ _____ ವಯಸ್ಸು _____ವರ್ಷಗಳು, ಸಾಮಾನ್ಯವಾಗಿ ನಿವಾಸಿಸುವ ಸ್ಥಳದ ಹೆಸರು_____, ಇಲ್ಲಿ ಹೇಳಿದ್ದೇನೆ/ಘೋಷಿಸುತ್ತೇನೆ ಡಾಕ್ಟರ್ ಹೆಸರು DR KEZIA ANNA JACOB ಅವರು ಆಸ್ಪತ್ರೆ ಹೆಸರು SHRI BM PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE ಅವರು ನನ್ನನ್ನು ಪೂರ್ಣವಾಗಿ ಪರೀಕ್ಷಿಸಿದರು ದಿನಾಂಕದಲ್ಲಿ____ ಸ್ಥಳ ಹೆಸರು_____ ಮತ್ತು ನನಗೆ ನನ್ನ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ ನಾನು ಒಂದು ರೋಗ (ಸ್ಥಿತಿ) ಅನುಭವಿಸುತ್ತಿದ್ದೇನೆ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ಅವರು ಒಂದು ಪದ್ಧತಿ/ಸಂಶೋಧನೆ ನಡೆಸುತ್ತಿದ್ದಾರೆ ಶೀರ್ಷಿಕೆಯುಳ್ಳ EVALUATION OF MUCIN 1 EXPRESSION AND ITS CORRELATION WITH GRADING AND STAGING IN COLORECTAL CARCINOMA ಡಾಕ್ಟರ್ DR SUREKHA U. ARAKERI ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ಕೇಳಿದ್ದಾರೆ ಅಧ್ಯಯನದಲ್ಲಿ.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ಈ ಕ್ರಮದ ನಡುವಲ್ಲಿ ಪ್ರತಿಕೂಲ ಫಲಿತಾಂಶಗಳನ್ನು ಎದುರಿಸಬಹುದು. ಮೇಲೆ ಹೇಳಿದ ಪ್ರಕಟಣೆಗಳಲ್ಲಿ, ಅಧಿಕಾಂಶವು ಚಿಕಿತ್ಸಿಸಬಹುದಾದರೂ ಅದನ್ನು ನಿರೀಕ್ಷಿಸಲಾಗುತ್ತಿಲ್ಲ ಆದ್ದರಿಂದ ನನ್ನ ಸ್ಥಿತಿಯ ಹಿರಿದಾಗುವ ಅವಕಾಶವಿದೆ ಮತ್ತು ಅಪರೂಪದ ಸಂದರ್ಭಗಳಲ್ಲಿ ಅದು ಮರಣಕಾರಕವಾಗಿ ಪರಿಣಮಿಸಬಹುದು ಹೊಂದಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಯಥಾಶಕ್ತಿ ಚಿಕಿತ್ಸೆ ಮಾಡಲು ಹೊಂದಿದರೂ, ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಈ ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳ ಮೌಲ್ಯಮಾಪನದಲ್ಲಿ ಸಹಾಯಕವಾಗುತ್ತದೆ ಇತರ ಸಮಾನ ಪ್ರಕರಣಗಳ ಚಿಕಿತ್ಸೆಗೆ ಉಪಯುಕ್ತ ಉಲ್ಲೇಖವಾಗಿದೆ, ಮತ್ತು ನಾನು ಅನುಭವಿಸುವ ರೋಗದಿಂದ ವಿಮುಕ್ತಿ ಅಥವಾ ಗುಣಮುಖಗೊಳ್ಳುವಲ್ಲಿ ನನಗೆ ಪ್ರಯೋಜನವಾಗಬಹುದು.

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ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿ, ಮಾಡಿದ ಪರಿಶೀಲನೆಗಳು / ಫೋಟೋಗ್ರಾಫ್‌ಗಳು / ವೀಡಿಯೋ ಗ್ರಾಫ್‌ಗಳು ನನ್ನ ಮೇಲೆ ತೆಗೆದುಕೊಳ್ಳಲಾಗುವ ಅನ್ವೇಷಕರು ರಹಸ್ಯವಾಗಿ ಇಡುವರು ಮತ್ತು ನಾನು ಅಥವಾ ನನಗೆ ಕಾನೂನು ದೃಷ್ಟಿಯಲ್ಲಿ ಸಂಬಂಧಿತರನ್ನು ಹೊರತುಪಡಿಸಿ ಇತರ ವ್ಯಕ್ತಿಯಿಂದ ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದಿಲ್ಲ. ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಶುದ್ಧವಾಗಿ ಸ್ವೇಚ್ಛಾಯಿತ, ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿಯ ಆಧಾರದ ಮೇಲೆ, ಚಿಕಿತ್ಸೆ / ಅಧ್ಯಯನದ ಸಂಬಂಧದಲ್ಲಿ ರೋಗನಿರ್ಧಾರ, ಚಿಕಿತ್ಸೆಯ ವಿಧಾನ, ಚಿಕಿತ್ಸೆಯ ಫಲಿತಾಂಶ ಅಥವ ಭವಿಷ್ಯದ ಪ್ರವೃತ್ತಿಗಳು ಬಗ್ಗೆ ಯಾವುದೇ ಸ್ಪಷ್ಟತೆ ಕೇಳಬಹುದು. ಅದೇ ಸಮಯದಲ್ಲಿ ನನಗೆ ತಿಳಿಸಲಾಗಿದೆ ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ನಿಲ್ಲಿಸಬಹುದು ನಾನು ಬಯಸಿದರೆ ಅಥವಾ ಅನ್ವೇಷಕರು ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನನ್ನನ್ನು ನಿಲ್ಲಿಸಬಹುದು.

ಪ್ರಬಂಧ ಅಥವಾ ಸಂಶೋಧನೆಯ ಸ್ವಭಾವ, ಮಾಡಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಚಿಕಿತ್ಸೆಯ ವಿಧಾನವನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡು, ನಾನು ಕೆಳಗಿನ ಶ್ರೀ / ಶ್ರೀಮತಿ_____ ನನ್ನ ಪೂರ್ಣವಾದ ಪ್ರಜ್ಞೆಯ ಸ್ಥಿತಿಯಲ್ಲಿ ಹೇಳಿದ ಸಂಶೋಧನೆ / ಪ್ರಬಂಧದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ.

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1)

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ANNEXURE- III

PROFORMA FOR STUDY

Name**:** **:** OP/IP NO **:**

Age **:**

Sex **:**

Occupation **:**

Residence **:**

Presenting Complaints :

Past History :

Personal History :

Family History :

Treatment History :

GENERAL PHYSICAL EXAMINATION:

Built Poor/Average/Well

Pallor Present/Absent

Icterus Present/Absent

Clubbing Present/Absent

Lymphadenopathy Present/Absent

Vitals: PR: RR:

BP: Temperature: Weight:

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SYSTEMIC EXAMINATION:

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

HISTOPATHOLOGICAL EXAMINATION OF RESECTED SPECIMENS-

GROSS MORPHOLOGY:

MICROSCOPY:

GRADING:

STAGING:

IMMUNOHISTOCHEMISTRY

TABLE 1: IMMUNOHISTOCHEMISTRY SCORING OF MUC1 EXPRESSION: -

SCORE	STAINING PATTERN	MUC1 PROTEIN EXPRESSION
0	0% of tumour cells	Negative
1+	<10% of tumour cells with weak positivity	Negative
2+	10-50% of tumour cells with moderate positivity	Equivocal
3+	>50% of tumour cells with strong positivity	Positive

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TABLE 2: MUC 1 EXPRESSION CORRELATION WITH CLINICAL VARIABLES (AGE, SEX, TUMOUR SITE), HISTOLOGICAL TYPES OF ADENOCARCINOMA, GRADING AND STAGING OF THE TUMOUR WILL BE DONE AS BELOW :-

S.No	**Clinical variables**	**(n=40)**	**MUC-1 IHC SCORE**		
1.	**Gender**		**Positive**	**Equivocal**	**Negative**
	Male				
	Female				
2.	**Age**				
	>60				
	≤60				
3.	**Tumour site**				
4.	**Histological subtypes**				
	Adenocarcinoma				
	Mucinous Adenocarcinoma				
	Signet ring cell carcinoma				

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5.	**Tumour differentiation**				
	Well				
	Moderately				
	Poorly				
6.	**Lymph node metastasis**				
	Yes				
	No				
7.	**Staging**				
	Stage I				
	Stage II				
	Stage III				
	Stage IV				

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KEY TO MASTER CHART

S. No	-	Serial Number
HPR No.	-	Histopathology Number
M	-	Male
F	-	Female
HPR Diagnosis	-	Histopathology Diagnosis

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MASTER CHART

S.NO.	HPR NO.	**AGE**	**SEX**	**CLINICAL PRESENTATION**	**GROSS MORPHOLOGY**	**SITE**	**HPR DIAGNOSIS**	**HISTOLOGICAL TYPES**	**HISTOLOGICAL GRADING**	**DEPTH OF INVASION**	STAGING	LYMPH NODE STATUS	**LYMPHOVASCULAR INVASION**	**MUC1 SCORE**
1	4091	45	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- CAECUM, ILEUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	3
2	1203	45	M	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- CAECUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	3
3	404	56	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	3
4	1491	60	M	OBSTRUCTIVE SYMPTOMS	CIRCUMFERENTIAL	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	2
5	209	65	M	MASS PER ABDOMEN and per rectal bleeding	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT3N1bMx	3	YES	2
6	6816	78	F	OBSTRUCTIVE SYMPTOMS	CIRCUMFERENTIAL	COLON	WELL DIFFERENTIATED ADENOCARCINOMA- DESCENDING COLON	ADENOCARCINOMA	WELL DIFFERENTIATED	SEROSA	pT2NxMx	0	NO	2
7	3277	62	F	OBSTRUCTIVE SYMPTOMS	CIRCUMFERENTIAL	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA - SIGMOID COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT3N0Mx	0	YES	3

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8	528	28	M	MASS PER ABDOMEN	CIRCUMFERENTIAL	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N2Mx	4	YES	3
9	4991	72	F	OBSTRUCTIVE SYMPTOMS	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - RECTOSIGMOID JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT3N1a	1	NO	3
10	6431	70	F	ABDOMINAL PAIN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA - COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	3
11	173	51	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- SIGMOID COLON AND RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N1b	2	YES	3
12	4954	65	M	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	RECTUM	MUCINOUS ADENOCARCINOMA- RECTUM	MUCINOUS ADENOCARCINOMA	POORLY DIFFERENTIATED	SEROSA	pT3N0	0	NO	3
13	8461	65	M	MASS PER ABDOMEN	EXOPHYTIC	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT4N1bM0	3	YES	3
14	738	60	M	MASS PER ABDOMEN AND PER RECTAL BLEEDING	ULCEROPROLIFERATIVE	RECTUM	SIGNET RING CELL CARCINOMA OF RECTUM	SIGNET RING CELL CARCINOMA	POORLY DIFFERENTIATED	SEROSA	pT3N2b	11	YES	3
15	1620	72	F	MASS PER ABDOMEN AND PER RECTAL BLEEDING	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	YES	2
16	1695	45	M	ABDOMINAL PAIN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- ASCENDING COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBMUCOSA	pT1N0Mx	0	NO	1
17	6918	80	M	MASS PER ABDOMEN AND PER RECTAL BLEEDING	CIRCUMFERENTIAL	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT3N1aMx	1	YES	3

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18	7133	65	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- CAECUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT4bN2b	7	YES	3
19	2557	46	F	OBSTRUCTIVE SYMPTOMS	EXOPHYTIC	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT2N0Mx	0	NO	2
20	3197	47	F	ABDOMINAL PAIN	EXOPHYTIC	COLON	WELL DIFFERENTIATED ADENOCARCINOMA- DESCENDING COLON	ADENOCARCINOMA	WELL DIFFERENTIATED	SEROSA	pT3N0Mx	0	NO	1
21	2603	37	F	OBSTRUCTIVE SYMPTOMS	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- DESCENDING COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT3N0Mx	0	NO	2
22	2616	74	M	ABDOMINAL PAIN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT2N1a	1	YES	3
23	1734	58	F	MASS PER ABDOMEN AND PER RECTAL BLEEDING	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT3N1Mx	1	NO	3
24	1377	48	F	MASS PER ABDOMEN AND PER RECTAL BLEEDING	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	NO	3
25	5624	38	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT3NxMx	0	NO	3
26	4803	56	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	RECTUM	MUCINOUS ADENOCARCINOMA- RECTUM	MUCINOUS ADENOCARCINOMA	POORLY DIFFERENTIATED	SUBSEROSA	pT3N2a	5	YES	3
27	5052	42	M	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- SIGMOID COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT2N1a	1	NO	3

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28	4763	67	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- ILEOCAECAL JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT4N1	2	YES	3
29	7402	76	M	MASS PER ABDOMEN	CIRCUMFERENTIAL	COLON	WELL DIFFERENTIATED ADENOCARCINOMA- SIGMOID COLON	ADENOCARCINOMA	WELL DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	NO	3
30	475	63	F	MASS PER ABDOMEN	POLYPOIDAL	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- TRANSVERSE COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	NO	3
31	420	73	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- ILEOCAECAL JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0Mx	0	YES	1
32	5834	35	F	MASS PER ABDOMEN AND PER RECTAL BLEEDING	CIRCUMFERENTIAL	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT2N1a	9	NO	2
33	6158	48	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA- RECTOSIGMD JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT4bN0	0	NO	2
34	4203	43	M	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA WITH MUCINOUS COMPONENT- CAECUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SEROSA	pT3N1aMx	1	NO	3
35	5602	60	M	MASS PER ABDOMEN	CIRCUMFERENTIAL	COLON	MODERATELY DIFFERENTIATED ADENOCARCINOMA- COLON	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT3N0	0	NO	3
36	6686	44	F	MASS PER ABDOMEN	EXOPHYTIC	RECTUM	WELL DIFFERENTIATED ADENOCARCINOMA-RECTUM	ADENOCARCINOMA	WELL DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	YES	3

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37	3922	80	M	MASS PER ABDOMEN AND PER RECTAL BLEEDING	ULCEROPROLIFERATIVE	RECTUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - RECTUM	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	NO	2
38	4522	73	M	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - ILEOCECAL JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	SUBSEROSA	pT3N0Mx	0	NO	3
39	302	50	M	MASS PER ABDOMEN	POLYPOIDAL	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - ILEOCECAL JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	NO	3
40	3102	66	F	MASS PER ABDOMEN	ULCEROPROLIFERATIVE	CAECUM	MODERATELY DIFFERENTIATED ADENOCARCINOMA - ILEOCECAL JUNCTION	ADENOCARCINOMA	MODERATELY DIFFERENTIATED	MUSCULARIS PROPRIA	pT2N0	0	NO	3

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