DISSERTATION ON

HISTOPATHOLOGICAL ANALYSIS AND p53 EXPRESSION IN INTESTINAL TUMORS

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CERTIFICATE

This is to certify that this dissertation titled **"HISTOPATHOLOGICAL ANALYSIS AND p53 EXPRESSION IN INTESTINAL TUMORS"** is the bonafide record work done by **Dr. A. Arputham** submitted as partial fulfillment for the requirements of M.D. Degree Examinations Branch III Pathology to be held in April 2013.

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CONTENTS

ABBREVIATIONS

1. TNM	-	Tumour Node Metastasis
2. GIST	-	Gastrointestinal stromal tumour
3. FAP	-	Familial adenomatous polyposis
4. HNPCC	-	Hereditary non polyposis colorectal cancer syndrome
5. AIDS	-	Acquired immunodeficiency syndrome
6. MSI	-	Microsatellite instability
7. CIN	-	Chromosomal instability
8. AJCC	-	American joint committee on cancer
9. APC	-	Adenomatous polyposis coli
10.GNMT	-	Glandular neuroendocrine mixed tumour
11.EGFR	-	Epidermal growth factor receptor
12.WHO	-	World Health Organization
13.EC	-	Enterochromaffin cell
14.PP	-	Pancreatic polypeptide
15.PYY	-	Polypeptide YY
16.MALT	-	Mucosa-associated lymphoid tissue.

INTRODUCTION

Colorectal cancer ranks second among the most common tumours of the world according to world cancer report 2000.[59] There is worldwide variation in the distribution of intestinal neoplasm, which appear largely due to exogenous factors rather than genetic.[52]

Colorectal carcinomas are uncommon in our country when compared with the western world. The incidence in India is about 7 / 100000.[18]

Curiously the small intestine is an uncommon site for tumour, despite its great length and vast pool of dividing cells.[9] Small bowel tumours account for 1-2% of all gastrointestinal neoplasms.[36] Small intestine tumours are usually asymptomatic or present with vague symptoms. If a small intestinal tumour is symptomatic there is 75% chance that it is malignant. The symptoms when present are usually mild and chronic. This is because of distensibility of small bowel. Intestinal obstruction when present is chronic and intermittent. Bleeding from the tumours though present in 25% is usually mild.

Majority of Colorectal carcinomas remain asymptomatic for years. They most often present with fatigue and weakness as these bulky lesions bleed readily and cause anemia.[9]

The treatment of choice for colorectal carcinoma is surgical resection. The postoperative outcome, prognosis and need for adjuvant therapy rely on the pathological assessment of resected specimen.

The vital elements of the pathological assessment of colorectal carcinoma specimen include pathological determination of TNM stage, tumour type, histological grade, resected margin and vascular invasion.[13]

In this retrospective study of intestinal tumours, incidence with respect to age, sex, site, and histomorphological features of various tumours were studied.

The present study also evaluates the role of tumour suppressor gene protein p53 in intestinal neoplasms and its prognostic value in colorectal adenocarcinomas.

The recent literature regarding intestinal tumours were also reviewed and correlated.

AIM OF THE STUDY

Specimens were analysed to find out:-

1. The incidence of intestinal neoplasms.
2. To evaluate the age, sex and site distribution of intestinal neoplasms.
3. To evaluate the histopathological features of intestinal neoplasms.
4. To assess the level of expression of p53 in intestinal neoplasms.
5. To correlate the level of P53 expression with the stage of the colorectal adenocarcinomas and to assess its prognostic value in colorectal adenocarcinomas.

MATERIALS AND METHODS

Out of 11891 cases reported totally at Thanjavur medical college, 111 cases of intestinal neoplasms was diagnosed during the period of January 2010 to June 2012 were included in this study.

Out of 111 specimens 62 were resected specimens and 49 were endoscopic biopsies. Detailed histories with attention to age, sex, symptoms, colonoscopic findings, specific site of lesions were analysed.

The endoscopic biopsy materials were submitted intoto for routine histopathological examination. Multiple bits from the tumours in resected specimens and the adjacent resected margins were submitted as per standard guidelines for histopathological study.

HISTOPATHOLOGICAL STUDY OF INTESTINAL NEOPLASMS:

All the specimens were fixed in 10% neutral formalin and were subjected to histopathological examination. Sections of 3-5µ thickness were made and routine staining with hematoxycilin and eosin was done (Appendix 1).

Staging of colorectal adenocarcinoma was done according to TNM staging.

p53 IMMUNOEXPRESSION:

A total of 30 cases of colorectal adenocarcinomas and 7 cases of small intestinal neoplasms were selected for studying the p53 expression. Tissue sections of 4μ thickness were fixed in formalin, paraffin embedded and stained with antibody directed against p53 antigen using an advanced polymer staining system.

Staining was performed according to the immunohistochemical staining protocol (Appendix 2). Under 400X magnification tumour cells were calculated by counting the number of brown stained tumour nuclei among the total number of cells in the intensely stained area and expressed in percentage.

p53 immunostaining was done. For small intestinal malignancy, all p53 positive nuclei were counted and the following semi-quantitative method was used: [±] – negative or equivocal (5% positive cells), [+] – weak\moderate (5-50% positivity) and [++] – intensely positive (>50% positivity).[15] For large intestinal malignancy, the slide was scored as positive if ≥10% of malignant nuclei were stained and was scored as negative if <10% of the nuclei were stained. While if fewer than 10% of the nuclei were stained, the slide was scored as negative.[28] The statistical analysis was performed to determine whether p53 protein expression was correlated with the stage of the colorectal adenocarcinomas. Statistical analysis

was carried out with the aid of Chi-square test (Java script package). P value of less than 0.05 was taken to indicate statistical significance.

REVIEW OF LITERATURE

HISTORICAL ASPECTS

Neoplasms of the small intestine have been very rare and first recognized in 1655. Neoplasm of small intestine, when Wesner reported a case of leiomyosarcoma[73], was first clinically reported in 1765. Carcinoids are common tumours of intestine and appendix. The cell of origin of these tumours was described by Nicholas kulchitsky[54].

In 1926, Dukes noted the association between polyposes of the colon and carcinoma. In 1940, he gave a system for grading carcinoma of colon based on the extent of invasion and lymphatic spread [21,73]. In 1977 the WHO proposed a scheme for histological typing of colorectal tumours.[74]

ANATOMY[8,20]

SMALL INTESTINE

It extends from the pylorus to ileocaecal junction and is about six meters in length. It is divided into

- Duodenum
- Jejunum
- Ileum

DUODENUM:

It is mostly retroperitoneum except at its two ends where it is suspended by folds of peritoneum. It is 25 inches long and extends from pylorus to duodeno-jejunal flexure.

JEJUNUM AND ILEUM:

They are suspended from the posterior abdominal wall by the mesentry. The jejunum constitutes the upper $2/5^{th}$ of the mobile part, while the ileum constitutes the lower $3/5^{th}$. The jejunum begins at duodeno-jejunal flexure and ileum ends at ileo-caecal junction.

LARGE INTESTINE

It extends from ileo-caecal junction to the anus. It is about 1.5 metre long and is divided into caecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, the rectum and the anal canal. In the angle between the caecum and the ileum, there is a narrow diverticulum called the vermiform appendix. The greater part of large intestine is fixed, except for appendix, transverse colon and sigmoid colon.

HISTOLOGY

The wall of the gastrointestinal tract is made up of the following layers:

A. Mucous membrane

- Lining epithelium
- Lamina propria
- Muscularis mucosa

B. Submucosa

C. Muscularis propria

D. Serosa

SMALL INTESTINE:

The mucosa shows villi and crypts lined by columnar cells. In ileum the entire lamina propria is infiltrated by lymphocytes forming follicle called Peyer's patch. The submucosa in duodenum has Brunner's glands lined by mucus secreting columnar cells, whereas in jejunum occasional lymphoid nodule may be present. The muscularis propria has inner circular and outer longitudinal layers of smooth muscles and is covered by the serosa.

LARGE INTESTINE:

The mucosa shows numerous crypts lined by columnar cells, amongst which are numerous goblet cells. The muscularis mucosa, submucosa and circular muscle coat are similar to small intestine. However the longitudinal muscle coat is gathered into three thick bands called taenia coli.

SMALL INTESTINAL TUMOURS

CLASSIFICATION (WHO):

Epithelial tumours

- Adenoma
  - Villous
  - Tubular
  - Tubulovillous
- Intraepithelial neoplasia(dysplasia)
  - Low-grade glandular intraepithelial neoplasia
  - High-grade glandular intraepithelial neoplasia
- Carcinoma
  - Adenocarcinoma
  - Signet-ring cell carcinoma

- Mucinous adenocarcinoma
- Small cell carcinoma
- Squamous cell carcinoma
- Medullary carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma

- Carcinoid
  - Gastrin cell tumour, functioning or non functioning
  - EC-cell, serotonin-producing tumour
  - Somatostatin cell tumour
  - Gangliocytic paraganglioma
  - L-cell, giucagon-like peptide and PP/PYY producing neoplasm
  - Mixed carcinoid-adenocarcinoma
  - Others

Non-epithelial tumours

- Leimyoma
- Leimyosarcoma
- Lipoma
- Gastro intestinal stromal tumour
- Kaposi sarcoma

- Angiosarcoma
- Others

Malignant lymphomas

- ❖ Immunoproliferative small intestinal disease
- ❖ Mantle cell lymphoma
- ❖ Western type B-cell lymphoma of MALT
- ❖ Burkitt lymphoma
- ❖ Diffuse large B-cell lymphoma
- ❖ Atypical Burkitt lymphoma
- ❖ Enteropathy associated T-cell lymphoma

Secondary tumours

Polyps

- Peutz-jeghers
- Juvenile
- Hyperplastic

INCIDENCE:

Small bowel tumours are relatively rare and constitute only 1-2% of all GI tumours, inspite of constituting 75% of the length and 90% of the mucosal surface of the alimentary tract. Approximately 2/3rd of small bowel tumours are malignant.

Mortality in small bowel neoplasm largely depends upon the histological subtypes and overall it was estimated to be 1040 deaths per year worldwide.[4]

Over 40 different histologically distinct tumours are known to be arising from the small intestine. However over 95% of these cases are adenocarcinoma, carcinoid, GIST or lymphoma.

The incidence of each histological type is adenocarcinoma – 24-44%, carcinoid tumour – 20-42%, sarcoma or GIST – 9%, lymphoma – 12-27%.

Adenocarcinoma and carcinoid tumours are the most common histological types.[85] The prevalence of asymptomatic tumours is much higher than predicted by the overall incidence reported.[10] There is an overall increase in incidence of adenocarcinoma and carcinoid tumours in recent years, particularly prominent in black males.[36,47]

ETIOLOGY:

Genetic and environmental conditions predispose to cancer of the small intestine.

PREDISPOSING CONDITIONS	HISTOLOGICAL TYPE
FAP	Adenocarcinoma
HNPCC	Adenocarcinoma
Celiac disease	Adenocarcinoma, Lymphoma
Gardner syndrome	Adenocarcinoma, Desmoid
Peutz-Jeghers	Adenocarcinoma, Hamartoma
Crohn's disease	Adenocarcinoma
AIDS	Lymphoma
Neurofibromatosis	Paraganglioma
History of primary cancer in other sites	Adenocarcinoma, Carcinoid

PATHOGENESIS OF SMALL INTESTINAL CARCINOMA:[33,39]

Tumours of Small bowel constitute to approximately 1 – 2% of the gastrointestinal malignancies.

Several theories have been forwarded to why small bowel is relatively protected from developing cancer:-

- The contents of the small bowel are liquid and therefore have a much faster transit time resulting in less time for exposure to potential carcinogens.

- Most carcinogens act under acidic conditions. The neutral to alkaline pH of small bowel makes it less susceptible to malignancy.
- Degradation of bile salts, which are carcinogenic in colon, is less due to decreased anaerobic bacteria in small intestine.
- High folate levels, which are protective against carcinogenesis, due to high receptors for folate uptake in small intestine.
- The small bowel has high levels of Benzopyrene hydroxylase, which leads to breakdown of Benzopyrene, a potential carcinogen used as food additive.
- The small bowel has high level of lymphoid tissue especially IgA, which may be immunoprotective against development of cancer.
- The small bowel has fewer stem cells, which may be the target for carcinogens.

MOLECULAR GENETICS:[44,50,55,78]

Tadashi Terada et al[78] p53 mutations are present in most of the primary carcinoma of the small intestine. Few studies emphasize that the oncogenes namely p53, K-ras, erbB2 and Cyclin-D1 are all altered in a manner similar to large bowel tumours. The role of the adenoma carcinoma sequence and the epidemiological factors for both small bowel colorectal adenocarcinoma, remain similar. It seems that the molecular genetic changes are common to both the tumours.[55]

An alteration in the p53 gene is the most common genetic event in the sporadic small intestine adenocarcinoma.[44] According to Ming Qing DU et al[50], p53 inactivation commonly caused by mutation and allele loss has shown to play an important role in the early development and/or the late disease progression of any human tumours including lymphoid malignancies and thus may also be important in MALT lymphoma genesis. This study also suggested that the development of low grade MALT lymphomas were associated with partial inactivation of p53 while high grade tumours show complete inactivation. Strong p53 immunoreactivity is seen in high grade MALT lymphomas whereas focal p53 positivity seen in low grade MALT lymphomas.

CLINICAL FEATURES:

No specific signs or symptoms indicate the presence of small intestinal malignancy. The typical presentation for these cancers is often vague and nonfocal. Most of the tumours present with symptoms of abdominal pain, weight loss and fatigability. These tumours can cause obstruction.[29]

A few generalizations can be made:-

1. It appears that malignant lesions are symptomatic earlier as opposed to benign lesions, which are discovered incidentally.[11]
2. Approximately half of all small bowel tumours present as an acute event, either as obstruction or perforation.[14]

EPITHELIAL TUMOURS

ADENOCARCINOMA:[33,39]

Adenocarcinomas of the small intestine are much rare than carcinoma of the large bowel. Obstruction occurs late because of the fluid nature of small bowel contents and tumours are often diagnosed at an advanced stage and carries poor prognosis. Most of the carcinomas arise within a pre-existing adenoma. The periampullary region of the duodenum is the most common site and patients present with jaundice and bleeding.

Macroscopic appearance:

The cancer may be flat, stenosing, ulcerative, infiltrative or polypoid. Usually cancer presents as an annular growth.

Microscopic appearance:

Majority of the adenocarcinomas are well differentiated to moderately differentiated. Mucinous adenocarcinomas do occur but signet-ring cell carcinomas are relatively rare and should be distinguished from secondaries, notably from stomach. Ampullary adenocarcinomas are mainly intestinal in type.

CARCINOID TUMOUR:[33,39,40]

They account for about 1/3rd of small intestinal tumours. Classical carcinoid tumours arise in the duodenum or ileum, usually in the 5th or 6th decades and are slightly more common in women. They may metastasize to liver and mesenteric nodes. The tumour secretes 5-hydroxy tryptamine and other vasoactive amines. It may give rise to carcinoid syndrome.

Carcinoid tumour may produce a variety of polypeptide hormones and are named according to the hormones produced.

i. Gastrinoma – Leads to multiple peptic ulcers of stomach, jejunum and ileum (Zollinger Ellison syndrome). Usually occurs in duodenum.
ii. Somatostatin cell tumour – Constitutes 15-20% of duodenal carcinoids. They are exclusively found in the region of ampulla of vater and are associated with Von Reckling Hausen disease.

Macroscopic features:

These tumours invade bowel wall to produce narrowing of lumen and appear yellow in colour following formalin fixation. They are often multiple and may be associated with a synchronous non-endocrine gastro intestinal tumour.

Microscopic appearance:

The tumour is composed of small cells with uniform round nuclei showing very frequent mitosis. Classical carcinoid consists of cells arranged in islands in

which the peripheral cells show palisading. Conspicuous among the peripheral cells are enterochromaffin cells. Other histologic patterns include trabecular, diffuse sheets, glandular structures, various intermediate forms and mixture of all these patterns.

Prognostic factors:

Histologic features are not useful in determining the prognosis. They are slow growing and less aggressive than adenocarcinoma. The larger tumours are more aggresive and show extensive local spread with ulceration and necrosis.

Special stains:

The EC cells are stained black with the argentaffin reaction, brick red by the diazo method and blue with lead hematoxylin.

Immunohistochemistry:

Positive reactions for chromogranin, neuron-specific enolase and PGP 9-5 will assist in the diagnosis of carcinoid tumour.

Electron microscopy:

It will demonstrate characteristic electron dense neurosecretory granules.

LYMPHOMAS:[32]

Primary small intestinal lymphomas contribute a major proportion (30-50%) among all the malignant tumours of small bowel, of which MALT lymphomas

form the most frequent type. On the contrary, Burkitt lymphoma is the most common tumour arising from the ileo-caecal region.

Burkitt lymphoma of small bowel:

Microscopically the neoplasm consists predominantly of intermediate sized cells admixed with neumerous tangible body macrophages. Tumour shows high mitotic activity.

Immunohistochemistry:

CD10, CD20, CD22 and CD79a – Positive

CD5 and CD23 – Negative

METASTATIC TUMOURS:

Metastatic tumours of small intestine are most frequently melanoma, carcinoma of lung, breast, colon and kidney.

Metastatic melanoma:[45]

Melanoma is composed of melanocytes of neuroectodermal origin. The most common metastatic tumour found in the gastrointestinal tract is malignant melanoma, of which the most frequently involved sites include small bowel (50%), colon (32%), and anorectum (25%). It presents as solitary or multiple polypoid lesions in the small intestine.

NON EPITHELIAL TUMOURS OF SMALL INTESTINE[33,39]

GIST:

Gastrointestinal stromal tumours are mesenchymal neoplasms that express c-kit. With rare exception 1/4th of GIST occurs in small intestine. The cell of origin is interstitial cell of cajal. They present clinically with pain, discomfort, obstruction or bleeding.

Macroscopic features:

GISTs are usually solitary, rounded or ovoid mass varying in size range from 2cm-20cm. On cross section they are circumscribed, lack a true capsule and reveal pink or grey cut surface with rubbery consistency.

Microscopic features:

They are categorized into

1. Spindle cell type
2. Epitheloid type
3. Mixed type

Immunohistochemistry:

Diagnosis of GIST is based on immunoreactivity for c-kit (CD117). Upto 60 – 70% of cases show expression of CD34 and 30 – 40% for SMA.

LIPOMA:[35]

Lipomas are rare but well recognized tumours of small and large intestine. Grossly appear as mass protruding into the lumen. Histologically the lesion consists of mature adipose tissue with various amounts of fibrous tissue.

LARGE INTESTINAL TUMOURS

COLORECTAL CARCINOMA

CLASSIFICATION (WHO):

Epithelial tumours

- Adenoma
  - Tubular
  - Villous
  - Tubulovillous
  - Serrated
- Intraepithelial neoplasia(dysplasia)
  - Low-grade glandular intraepithelial neoplasia
  - High-grade glandular intraepithelial neoplasia
- Carcinoma
  - Adenocarcinoma

- Small cell carcinoma
- Mucinous adenocarcinoma
- Squamous cell carcinoma
- Signet-ring cell carcinoma
- Medullary carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma

❖ Carcinoid (well differentiated endocrine neoplasm)

- EC-cell, serotonin-producing tumour
- L-cell, giucagon-like peptide and PP/PYY producing neoplasm
- Mixed carcinoid-adenocarcinoma
- Others

Non-epithelial tumours

- Lipoma
- Leimyoma
- Leimyosarcoma
- Gastro intestinal stromal tumour
- Kaposi sarcoma
- Angiosarcoma

- Malignant melanoma
- Others

Malignant lymphomas

- Mantle cell lymphoma
- Marginal zone B-cell lymphoma of MALT
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Atypical Burkitt lymphoma
- Others

Secondary tumours

Polyps

- Hyperplastic
- Peutz-jeghers
- Juvenile

INCIDENCE:

Colorectal carcinoma exhibits at least a 25 fold variation in occurrence worldwide. It is most common in the industrialized countries of western world and Eastern Europe, North America, Newzealand and Australia, while its incidence is low in Africa and Asia.[24]

ETIOLOGY:[24]

Individuals at high risk of developing colorectal carcinoma are:-

- History of colorectal adenoma
- Family history of colorectal carcinoma
- Family history of Hereditary non polyposis colon cancer
- Patients with Familial Adenomatous Polyposis, Gardner syndrome, Old field syndrome, Turcott syndrome, Zanca syndrome, Peutz-Jeghers syndrome, Juvenile polyposis syndrome, Ulcerative colitis, Crohn's disease

People taking high calorie diet along with sedentary life style habits are more prone to develop colorectal carcinoma. Statistical studies show that smoking, alcohol and animal fat consumption are the major predisposing factors.

Family history and physical inactivity are not strong contributions to the etiology of rectal cancers.[84] A rare but well recognized risk factor in colorectal tumour is therapeutic pelvic irradiation.[32] Non-steroidal anti-inflammatory drugs are known to be protective against colorectal carcinoma.[61]

PATHOGENESIS OF COLORECTAL CARCINOMA:

The majority of colorectal carcinoma develops sporadically (88-94%). The remainder occurs in high risk groups like hereditary cancer syndromes (e.g. HNPCC and FAP) and long standing inflammatory bowel disease.[17]

Genetic susceptibility:

Among colorectal carcinomas, 5-15% is hereditary in nature. Various genetic disorders exist, that predispose individuals to colorectal cancer.[19] According to genetic susceptibility, the colorectal carcinomas are broadly classified into familial adenomatous polyposis coli (FAP) and hereditary non polyposis colon cancer (HNPCC).[32]

Molecular genetics:

Molecular genetics varies for both proximal and distal colonic tumours. Proximal colonic tumours are associated with microsatellite instability whereas the distal colonic tumours are related to specific chromosomal instability.

Majority colorectal tumours begin with a mutational inactivation of the APC suppressor gene. Then additional genetic alteration like inactivation of tumour suppressor gene such as p53 and activation of proto-oncogene such as ras, c-myc occurs.

CLINICAL FEATURES:[9]

Few patients remain asymptomatic, being diagnosed during routine screening procedures. Anaemia and haematochezia are commonly seen in symptomatic individuals. Tumours in the proximal colon often grow as polypoid, exophytic masses; these tumours rarely cause obstruction. In contrast, carcinomas in the distal colon tend to be annular lesion and cause obstruction. Other symptoms include fever, abdominal pain, abdominal distension, malaise, weight loss, and tenesmus. Obstruction or perforation may complicate the clinical feature.

HISTOPATHOLOGICAL FEATURES OF COLORECTAL CARCINOMAS

ADENOCARCINOMA:

Macroscopic features:

Grossly most of the colorectal tumours present as either polypoid or ulcerative/infiltrating lesions. Mucinous adenocarcinomas exhibit a gelatinous, glaring appearance and often have areas with macroscopically visible layers of mucus.

Microscopic features:[32]

The characteristic feature of colorectal adenocarcinoma is invasion into the submucosa. Majority of the colorectal adenocarcinomas are gland forming

tumours. 90-95% of large bowel tumours are adenocarcinomas. 25% are well differentiated, 60% are moderately differentiated and 1.5% is poorly differentiated.

Grading of Colorectal Adenocarcinoma[69]			
Grade	**Descriptive nomenclature**	**Criteria**	**AJCC recommendation**
G_X	Grade cannot be assessed	--	--
G_1	Well differentiated	95% of gland forming	Low grade
G_2	Moderately differentiated	50% - 95% gland forming	Low grade
G_3	Poorly differentiated	<50% gland forming	High grade
G_4	Undifferentiated	No apparent gland formation	High grade

MUCINOUS ADENOCARCINOMA:[22,76]

Mucinous adenocarcinomas, including signet ring cell cancer account for approximately 10% of colorectal cancers. Usually it affects younger individuals, often seen in the proximal colon and It presents at an advanced stage. Presence of >50% mucinous area must be necessary to designate it as mucinous adenocarcinoma.

There are two subtypes of mucinous adenocarcinoma –

1. Signet ring cell carcinoma
2. Colloid carcinoma

Signet-ring cell carcinoma:

Signet-ring cell tumours account for approximately 1% of colorectal tumours. This designation is used if >50% of tumour cells contain intracytoplasmic mucin.[25] This variant behaves very aggressively and it has a poor prognosis. Many of the patients are young and the disease clinically resembles inflammatory bowel disease. Both small cell and signet ring cell carcinoma are consistently been found to have an adverse effect on prognosis irrespective of its stage. [75]

Colloid carcinoma:[76]

Colloid carcinomas often arise in villous adenomas. These are very large bulky tumours with large mucinous areas. Diagnostic features are:

1. Presence of abundant intraluminal mucin
2. Stroma contain pools of mucin
3. Superficial pools of mucin containing free lying ribbons or clusters of malignant cells.[76]

Histochemical, immunohistochemistry and electron microscopic features of colorectal adenocarcinoma:[39,40]

Histochemically large majority of colorectal adenocarcinomas are positive for alcian blue stains. Immunohistochemically MUC1 and MUC3 are expressed by conventional adenocarcinoma while MUC2 by mucinous carcinoma. All colorectal adenocarcinomas express villin, CK, CDX2, TAG-72 and LEA. Electron microscopy shows presence of prominent collection of microfilaments running perpendicular to the cell membrane and entering the brush border.

SMALL CELL CARCINOMA:[39]

Small cell carcinoma comprises <1% of colorectal cancer. Histologically they are identical to small cell carcinoma of the lung. They have extremely poor prognosis and almost all cases have lymphnode and liver metastasis.

SQUAMOUS AND ADENOSQUAMOUS CARCINOMA:[39]

These tumours are extremely rare. They have been associated with ulcerative colitis, schistosomiasis and pelvic irradiation.

STAGING OF COLORECTAL CARCINOMA

Once the diagnosis of colorectal carcinoma has been established by whatever method, accurate staging is of paramount importance in planning the surgical approach, in deciding whether neoadjuvant chemotherapy and radiotherapy is necessary and in determining the risk of recurrence and overall prognosis.[31]

Numerous schemes have been developed to stage colorectal carcinomas. The depth of invasion and the presence or absence of lymphnode involvement are the two major determinants of all staging systems.[24]

In 1932, Dukes refined the Lockhart and Mummery classification devised in 1926 and established the staging system that bears his name.

DUKE'S STAGING SYSTEM [24]

- Stage A – Tumour confined to the intestinal wall
- Stage B – Tumour invading through the intestinal wall
- Stage C – With lymphnode(s) involvement
    - C1 – Only the regional lymphnodes are involved
    - C2 – Nodes at the point of mesenteric blood vessel ligature are involved
- Stage D – with distant metastasis

Another staging system formerly widely used is that described by Astler and Coller which represents modification of classification proposed by Duke's and Kirklin.

ASTLER-COLLER STAGING SYSTEM[43]

- Stage A : Tumour limited to the mucosa
- Stage B1 : Tumour involving the muscularis externa but not penetrating it
- Stage B2 : Tumour penetrating through the muscularis externa
- Stage C1 : Tumour confined to the bowel wall with regional lymphnode metastases
- Stage C2 : Tumour penetrating through the wall with regional lymphnode Metastases
- Stage D : Distant metastases

In 1954, Denoix proposed the TNM cancer classification system based on disease extent. This classification is compatible with the Duke's classification but it adds greater precision in the identification of some of the prognostic subgroups.

In the TNM system, the designation

- T – The local extent of the primary tumour at the time of diagnosis, before the administration of treatment of any kind

- N – The status of regional lymphnodes
- M – Distant metastasis including the non-regional lymphnodes.
- p – Pathological determination of the TNM,[13].

Primary tumour (T)

- **pT_x** Primary tumour cannot be assessed
- **pT_0** No evidence of primary tumour
- **pT_{is}** Carcinoma in situ (intraepithelial or intramucosal carcinoma)
- **pT_1** Tumour invades the submucosa
- **pT_2** Tumour invades the muscularis propria
- **pT_3** Tumour invades through the muscularis propria into the subserosa or into the non-peritonealised pericolon or perirectal tissues
- **pT_4** Tumour directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b)

Regional Lymphnodes (N)

- **pN_x** Regional lymphnodes cannot be assessed
- **pN_0** No regional lymphnode metastasis
- **pN_1** Metastasis in 1 to 3 lymphnodes
- **pN_2** Metastasis in 4 or more lymphnodes

Distant Metastasis (M)

- **pM_x** Presence of distant metastasis cannot be assessed
- **pM_0** No distant metastasis
- **pM_1** Distant metastasis

TNM Stage groupings

Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
	T_2	N_0	M_0
Stage IIA	T_3	N_0	M_0
Stage IIB	T_4	N_0	M_0
Stage IIIA	T_1/T_2	N_1	M_0
Stage IIIB	T_3/T_4	N_1	M_0
Stage IIIC	Any T	N_2	M_0
Stage IV	Any T	Any N	M_1

CARCINOID TUMOUR:[39,40]

They can occur in any portion of large intestine but are more common in the rectum. Colorectal carcinoids are rarely associated with carcinoid syndrome.

Macroscopic appearance:

It may appear as a flat and slightly depressed plaque or as a polypoid lesion which has yellow colour after formalin fixation.

Microscopic appearance:

The tumour is characterized by small, uniform cells growing in a ribbon or festoon fashion in the stroma. The tumours are consistently argyrophilic but not usually argentaffinic. Immunohistochemically they stain for pan endocrine markers and for variety of peptide hormones.

ADENOCARCINOID (GLANDULAR NEURO ENDOCRINE MIXED TUMOUR):[88]

Colorectal GNMT is an uncommon entity affecting elderly patients with female to male ratio 1: 1.1 Histologically 58% of GNMT were classified as collision tumours and 42% were classified as composite tumours. Neuroendocrine and glandular components of the GNMT can show a spectrum of differentiation. Regardless of its percentage volume each component can metastasize separately.

Poorly differentiated component will likely metastasize and make an impact in prognosis.

LARGE INTESTINE LYMPHOMA:[25]

Lymphomas of large bowel are relatively rare with the most common site involved being caecum followed by rectum. Diffuse large B-cell lymphoma form the most common type followed by MALT lymphoma.

RECTAL MELANOMA:[67,71]

Malignant melanoma of rectum constitutes about 1% of anorectal malignancies. eyes and skin are the two most frequent sites for melanoma followed by rectum. It is very aggressive usually starting from the 4^{th} decade, predominantly in women with an increased incidence in the 5^{th} or 6^{th} decade of life. Patient often presents with rectal bleeding and tenesmus. Prognosis is very poor.

p53:

The Tp53 (Tumour protein p53, also abbreviated as p53) gene is located in chromosome 17p13.1. It is the single most common target for genetic alteration in human tumours. It plays an important role in cell cycle control and in the induction of apoptosis. It has been described as “the guardian of the genome”, “the guardian angel gene”, and “the master watchman” referring to its role in conserving stability by preventing genome mutation.

The p53 tumour suppressor gene is mutated in approximately 70-80% of colorectal carcinoma.[9] Mutation or loss of p53 usually occurs at the time of transition from adenoma to carcinoma in the adenoma-carcinoma sequence. The frequency of p53 abnormalities increases with the progression of the lesion. Mutation of the p53 tumour suppressor gene is thought to play an important role in the progression of colorectal carcinoma and might therefore represent a clinically useful marker of prognosis. Immunohistochemical markers currently being investigated for their prognostic impact include proteins involved in the wide array of signaling pathways mediating colorectal tumour progression and metastasis.

D.A. Spandidos et al[15] in his study of 13 human small intestinal tumours for p53 using an immunohistochemical technique, found that p53 nuclear phosphoprotein is overexpressed in 46% of small intestinal tumours including lymphoma(1), angiosarcoma of the jejunum(1), leiomyosarcoma(1), adenocarcinoma of the small intestine(1) and metastatic adenocarcinomas(2) of the colon. Intense p53 expression was observed only in the MALT lymphoma and the two metastatic adenocarcinomas of the colon. These results indicate that the p53 gene may be involved in the pathogenesis of small intestinal tumours.

Ge C, He S, Tian Y[27] in their study of the relationship of p53 gene mutation with the occurrence and prognosis of small intestinal tumours, 75% of small intestine cancers showed p53 positivity. One out of 7 cases of small bowel

adenoma only one was positive for p53 protein. Normal tissue of intestine did not express p53 protein. The degree of tumor cell differentiation, invasion, metastasis and prognosis significantly correlated with the degree of p53 protein expression.

Krugmann et al[41] studied clinicopathological and immunohistochemical features of 144 cases of primary gastrointestinal lymphoma with sufficient clinical followup. The expression levels of p53 were studied for prognostic significance. The lymphomas were classified as diffuse large B cell lymphoma or MALT lymphoma. High p53 accumulation was more prevalent in diffuse large B cell lymphoma. p53 expression was important in the transformation of low grade MALT lymphoma and is an indicator for aggressive behavior in high grade tumours.

Peter F. Rambau et al[65] studied p53 immunoreactivity in 109 patients with colorectal adenocarcinoma using immunohistochemistry by the use of monoclonal antibody. Out of 109 patients, 61 cases (56%) expressed p53 protein in the nucleus of malignant cells. It was expressed more in left sided colonic tumours ($p<0.05$) and this could support the hypothesis that right and left colonic tumours have different pathogenesis and probably also responsible for difference in prognosis in these two topographic sites.

Yuvan – Tzu Lan et al[87], in his study of 258 patients, reported that, p53 overexpression was found in higher frequency in well to moderately differentiated

tumours than poorly differentiated tumours. p53 overexpression was more frequent in patients with non-mucinous type of colorectal carcinoma (39.0 Vs 29.2%, p=0.344) than mucinous type of colorectal carcinoma.

T. Starzynska et al[77], in his study, concluded that p53 expression correlates well with the stage of the disease and unfavourable outcome. P53 overexpression was seen in tumours which had invaded regional lymphnodes. The increased level of p53 was associated with early relapse and death.

George E. Theodoropoulos et al[28] done a retrospective study of 164 colorectal adenocarcinoma specimens for p53 and EGFR expressions. The conclusion was p53 protein overexpression was significantly associated with advanced tumour stage (p=0.004).

Mohammad-Reza-Ghavam-Nasiri MD et al[51], in his study of 100 specimens for p53 protein using monoclonal antibody, concluded that p53 protein expression didn't show significant association with age, gender, site of tumour, histological type and stage of the disease.

Scott et al[72] analysed 52 colorectal carcinomas and found no correlation with p53 overexpression and several factors related to prognosis.

Recently Campo et al[7] in their study also found that p53 overexpression was not correlated with tumour grade, tumour stage in 64 cases of colorectal

adenocarcinomas. These authors concluded that p53 could not be used as prognostic marker.

It is evident from the above studies, that p53 overexpression as a prognostic marker in colorectal adenocarcinoma is controversial. This may be due to the differences in the numbers of tumours examined or the different kind of materials, methods and antibodies used in various studies.

In this study, the expression of p53 in various intestinal tumours received at the Department of Pathology, Thanjavur medical college has been studied and the results were compared with the above studies.

OBSERVATION AND RESULTS

INCIDENCE:

Out of the 4286 neoplasms diagnosed totally, during the period of study (January 2010 – June 2012), there were 111 neoplasms arising in the intestine. Thus the annual incidence of intestinal neoplasms in our study was 2.6% (Table 1).

TABLE – 1

INCIDENCE OF INTESTINAL NEOPLASMS IN OUR STUDY

Period	Total No. of specimens	Total neoplasms	Intestinal neoplasms	Incidence (%)
Jan 2010 – June 2012	11891	4286	111	2.6

TABLE – 2

INCIDENCE OF SMALL AND LARGE INTESTINE NEOPLASMS IN OUR STUDY

Total No. of neoplasms	Small intestine		Large intestine	
	No. of cases	%	No. of cases	%
111	11	10	100	90

Of the 111 intestinal neoplasms, 100 cases were from the large intestine which contributes significantly for higher incidence with 90% (Table 2) (Chart 1).

INCIDENCE OF SMALL AND LARGE INTESTINE NEOPLASMS

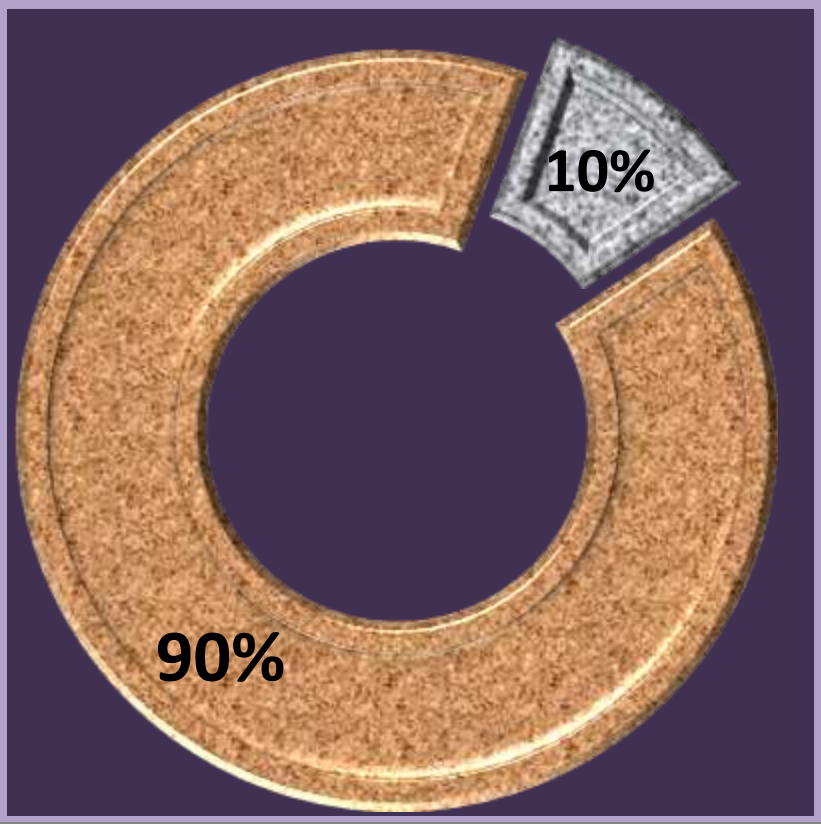


CHART: 1

INCIDENCE OF BENIGN AND MALIGNANT NEOPLASMS

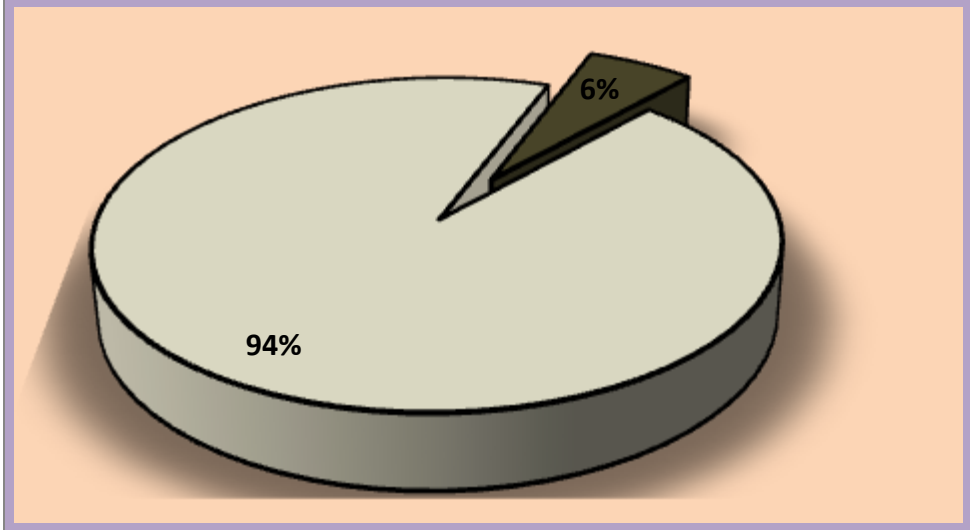


CHART: 2

TABLE – 3

INCIDENCE OF BENIGN AND MALIGNANT NEOPLASMS

TUMOUR TYPE	BENIGN		MALIGNANT	
	Small intestine	**Large intestine**	**Small intestine**	**Large intestine**
NO. OF CASES	2	5	9 (0.3%)	95 (2.99%)

Among 111 intestinal neoplasms 3/4th was malignant. Large intestinal tumours constitute 2.99% and small intestinal tumours 0.3% of 3174 cases of malignant tumours (Table 3) (Chart 2).

TABLE – 4

CLINICAL PRESENTATION OF SMALL INTESTINAL NEOPLASMS

SYMPTOMS	NO OF CASES	%
INTESTINAL OBSTRUCTION	8	73
BLEEDING PER RECTUM	1	9
ABDOMINAL MASS	1	9
ABDOMINAL PAIN	1	9

From the Table 4 (Chart 3), it is clear that most common clinical symptom of small intestinal neoplasm is intestinal obstruction (73%).

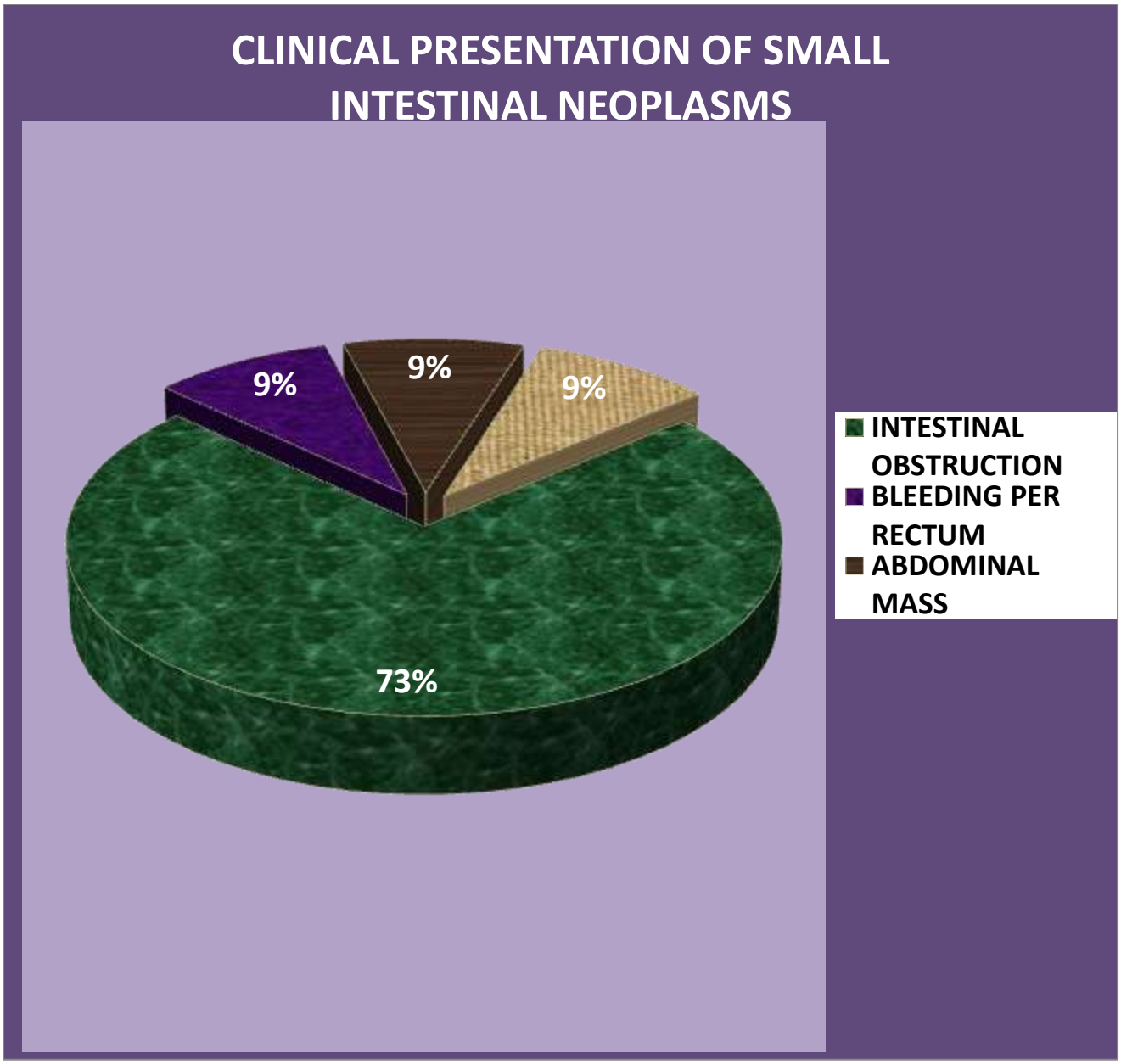

CLINICAL PRESENTATION OF SMALL INTESTINAL NEOPLASMS
9%
9%
9%
73%
INTESTINAL OBSTRUCTION
BLEEDING PER RECTUM
ABDOMINAL MASS

CHART: 3

TABLE – 5

SITE DISTRIBUTION OF SMALL INTESTINAL NEOPLASMS

SITE	NO OF CASES	%
DUODENUM	7	64
JEJUNUM	2	18
ILEUM	2	18
TOTAL	11	100

From Table 5 (Chart 4), it is clear that most of the small intestinal neoplasms arise from the duodenum (64%).

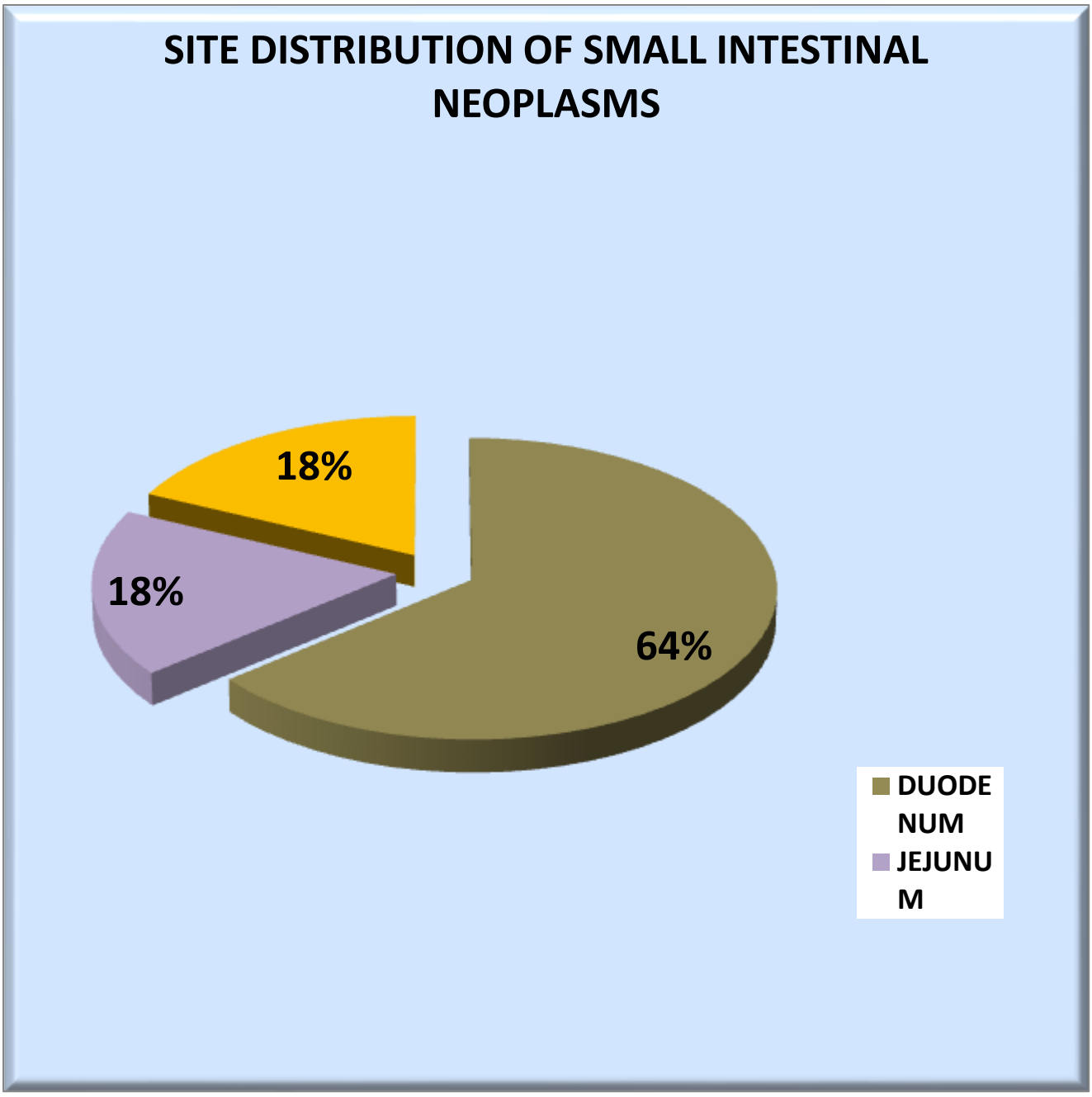

SITE DISTRIBUTION OF SMALL INTESTINAL NEOPLASMS
18%
18%
64%
DUODENUM
JEJUNUM

CHART: 4

TABLE – 6

AGE, SEX AND TYPE WISE DISTRIBUTION OF SMALL INTESTINAL NEOPLASMS

AGE (Yrs)	MALIGNANT									BENIGN		
	ADENOCARCINOMA (36%)			LYMPHOMA (36%)			METASTATIC TUMOUR (9%)					
	M	F	T	M	F	T	M	F	T	M	F	T
0-10	0	0	0	0	1	1	0	0	0	0	0	0
11-20	0	0	0	0	0	0	0	0	0	0	0	0
21-30	0	0	0	1	0	1	0	0	0	0	0	0
31-40	0	2	2	0	0	0	0	0	0	0	1	1
41-50	2	0	2	1	0	1	0	0	0	0	0	0
51-60	0	0	0	1	0	1	1	0	1	0	0	0
61-70	0	0	0	0	0	0	0	0	0	1	0	1
TOTAL	2	2	4	3	1	4	1	0	1	1	1	2

From our statistical study data, it is inferred that the small intestinal neoplasms commonly occur in the 30 – 50 years of age group and show equal incidence in both the sexes (Table 6). Of small intestinal malignant tumours adenocarcinoma and lymphoma have equal incidence in our study (Table 6) (Chart 5).

AGE AND TYPE WISE DISTRIBUTION OF SMALL INTESTINAL NEOPLASMS

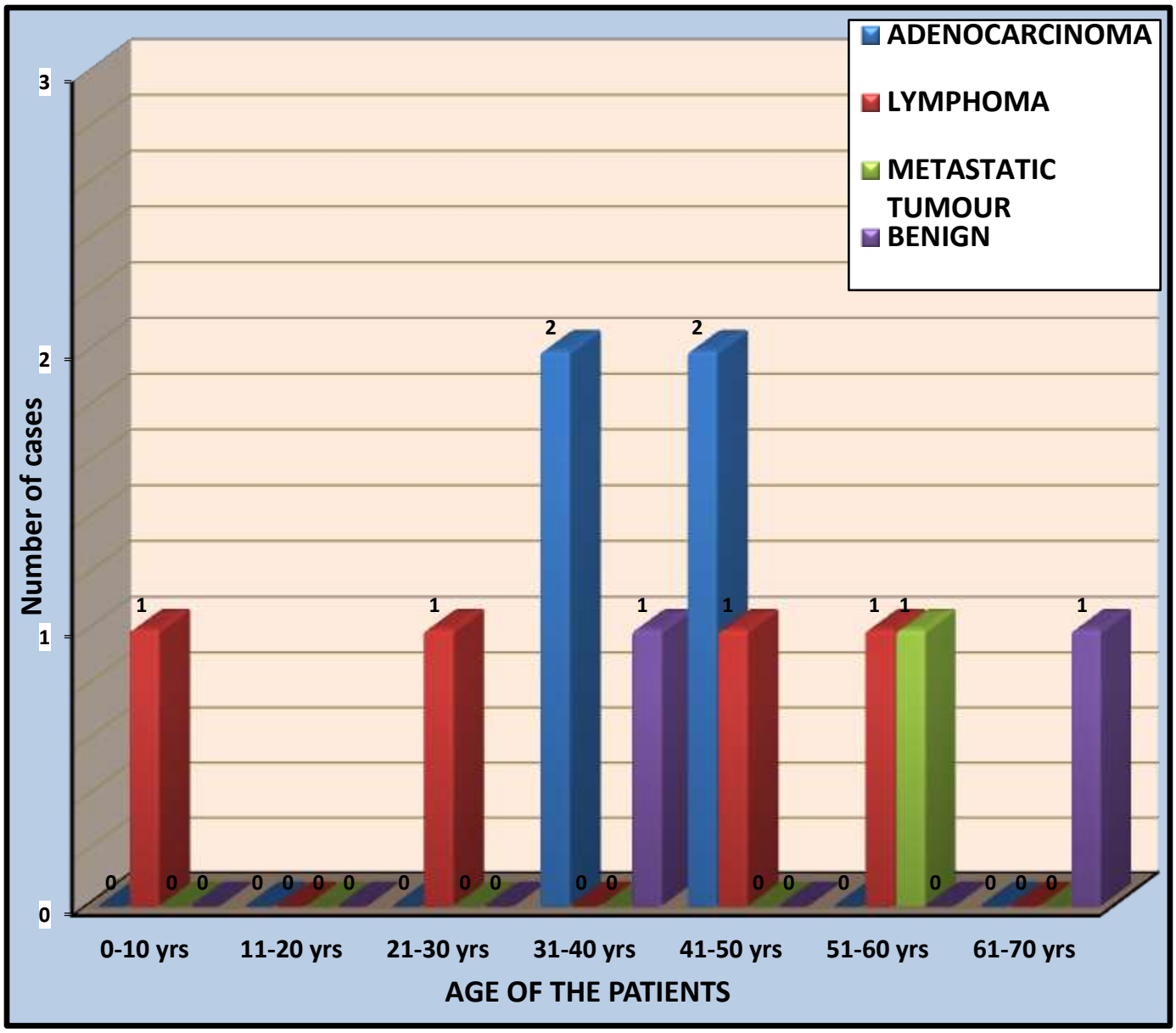


CHART: 5

TABLE – 7

p53 EXPRESSION IN SMALL INTESTINAL TUMOURS

S.NO	BIOPSY NO	HPE	GRADE	P53
1	381/11	BURKITT LYMPHOMA		-
2	888/11	ADENOCARCINOMA	II	+
3	1677/11	ADENOCARCINOMA	II	-
4	2092/11	ADENOCARCINOMA	I	+
5	4726/11	MALT-LYMPHOMA		+

TABLE – 8

p53 EXPRESSION IN RELATION TO HISTOLOGICAL TYPES

TUMOURS	p53				TOTAL
	+	%	-	%	
ADENOCARCINOMA	2	67	1	33	3
LYMPHOMA	1	50	1	50	2

In this study 60% of the small intestinal tumours revealed p53 positivity. 67% of the adenocarcinomas and 50% of the lymphomas showed immune reactivity for p53 protein (Table 8).

TABLE – 9

CLINICAL FEATURES OF COLORECTAL TUMOURS

SYMPTOMS	NO OF CASES	%
BLEEDING PER RECTUM	55	55%
LOSS OF WEIGHT	15	15%
CONSTIPATION	9	9%
INTERMITTENT CONSTIPATION AND LOOSE STOOLS	12	12%
INTESTINAL OBSTRUCTION	9	9%

Table 9 (Chart 6) shows that, among the clinical features, bleeding per rectum was the most common clinical presentation (55%) of the colorectal tumours.

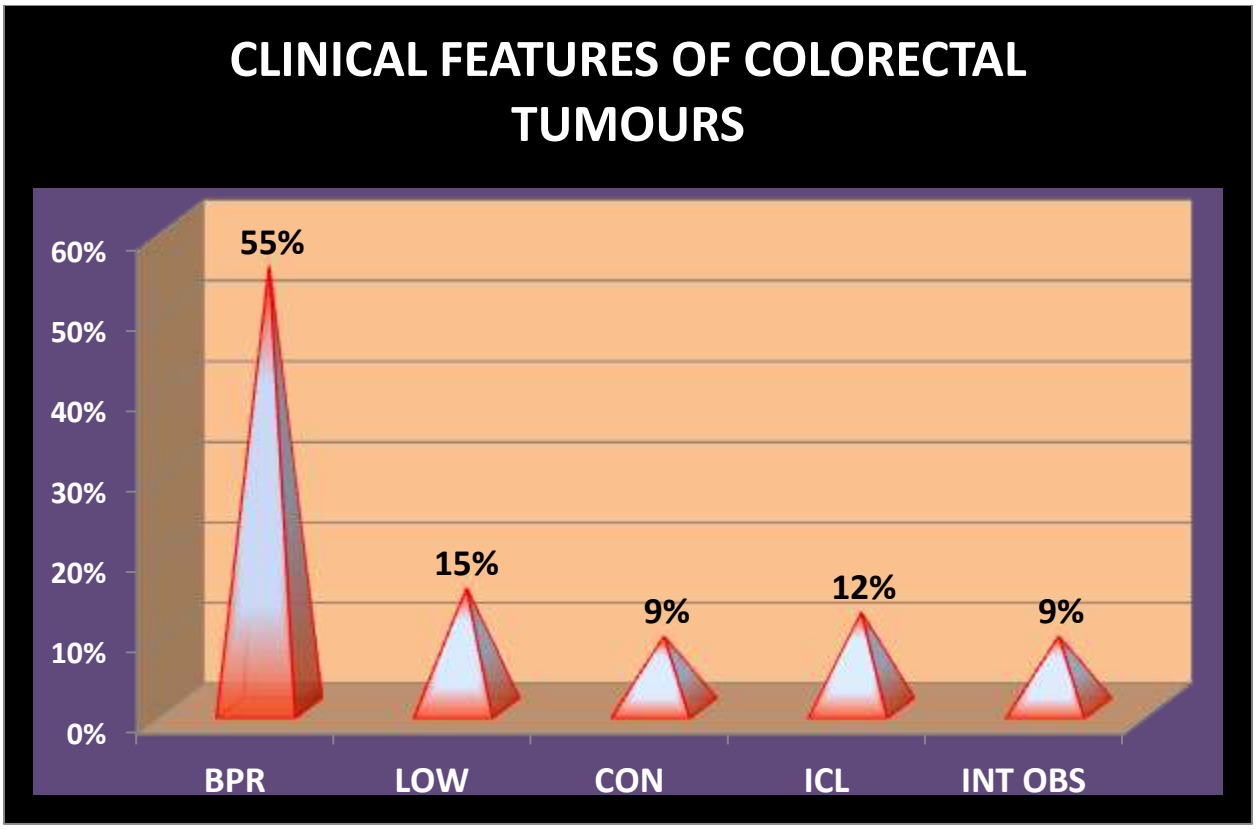

CLINICAL FEATURES OF COLORECTAL TUMOURS
60%
50%
40%
30%
20%
10%
0%
55%
15%
9%
12%
9%
BPR
LOW
CON
ICL
INT OBS

CHART: 6

TABLE – 10

COLONOSCOPIC FINDINGS OF COLORECTAL TUMOURS

COLONOSCOPIC FINDINGS	NO OF CASES	%
ULCEROPROLIFERATIVE	82	82
POLYP	10	10
NARROWING OF LUMEN	8	8
TOTAL	100	100

From Table 10 (Chart 7), it is evident that ulceroproliferative growth was the predominant (82%) gross feature in most of the colorectal tumours.

TABLE – 11

SITE DISTRIBUTION OF COLORECTAL TUMOURS

SITE	NO OF CASES	%
CAECUM	10	10
ASCENDING COLON	8	8
TRANSVERSE COLON	8	8
DESCENDING COLON	0	0
SIGMOID COLON	8	8
RECTUM	66	66
TOTAL	100	100

TABLE – 12

SITE DISTRIBUTION OF COLORECTAL TUMOURS IN RELATION TO SEX

SITE	MALE	FEMALE	TOTAL
CAECUM	2	8	10
ASCENDING COLON	6	2	8
TRANSVERSE COLON	7	1	8
DESCENDING COLON	0	0	0
SIGMOID COLON	5	3	8
RECTUM	44	22	66
TOTAL	64	36	100

From Table 11&12 (Chart 8&9), it is evident that rectum is the most common site of occurrence (66%) in both the sexes and colorectal tumours show male predominance.

COLONOSCOPIC FINDINGS IN COLORECTAL TUMOURS

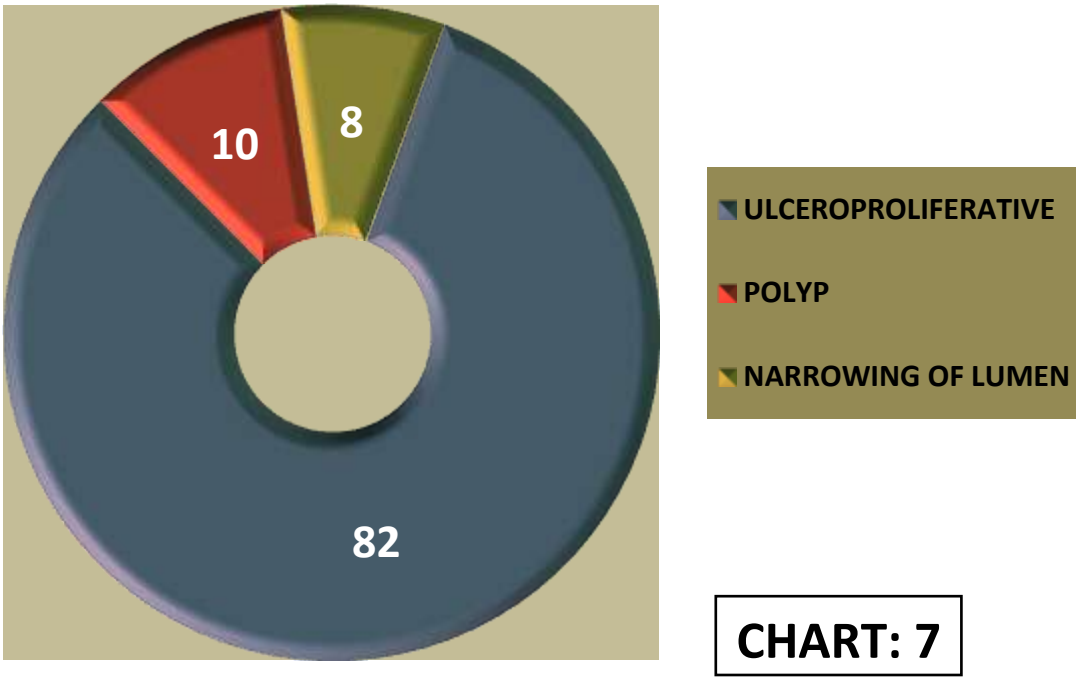


CHART: 7

SITE DISTRIBUTION OF COLORECTAL TUMOURS

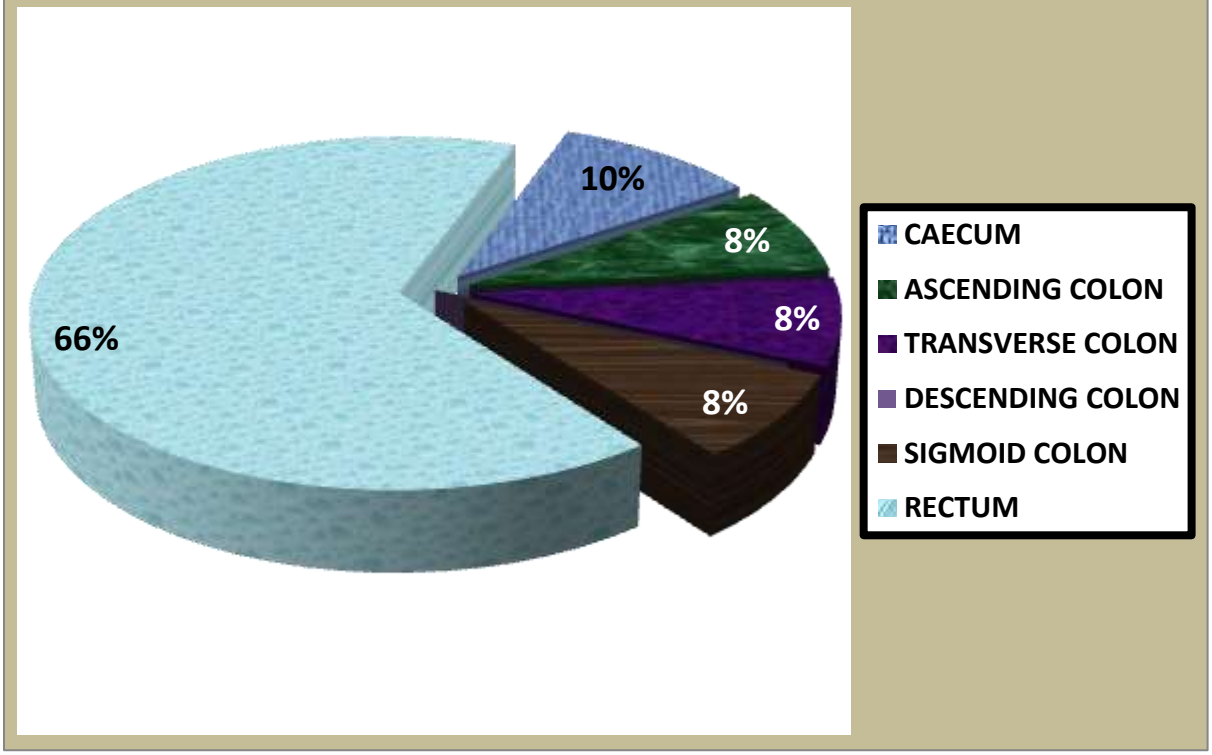


CHART: 8

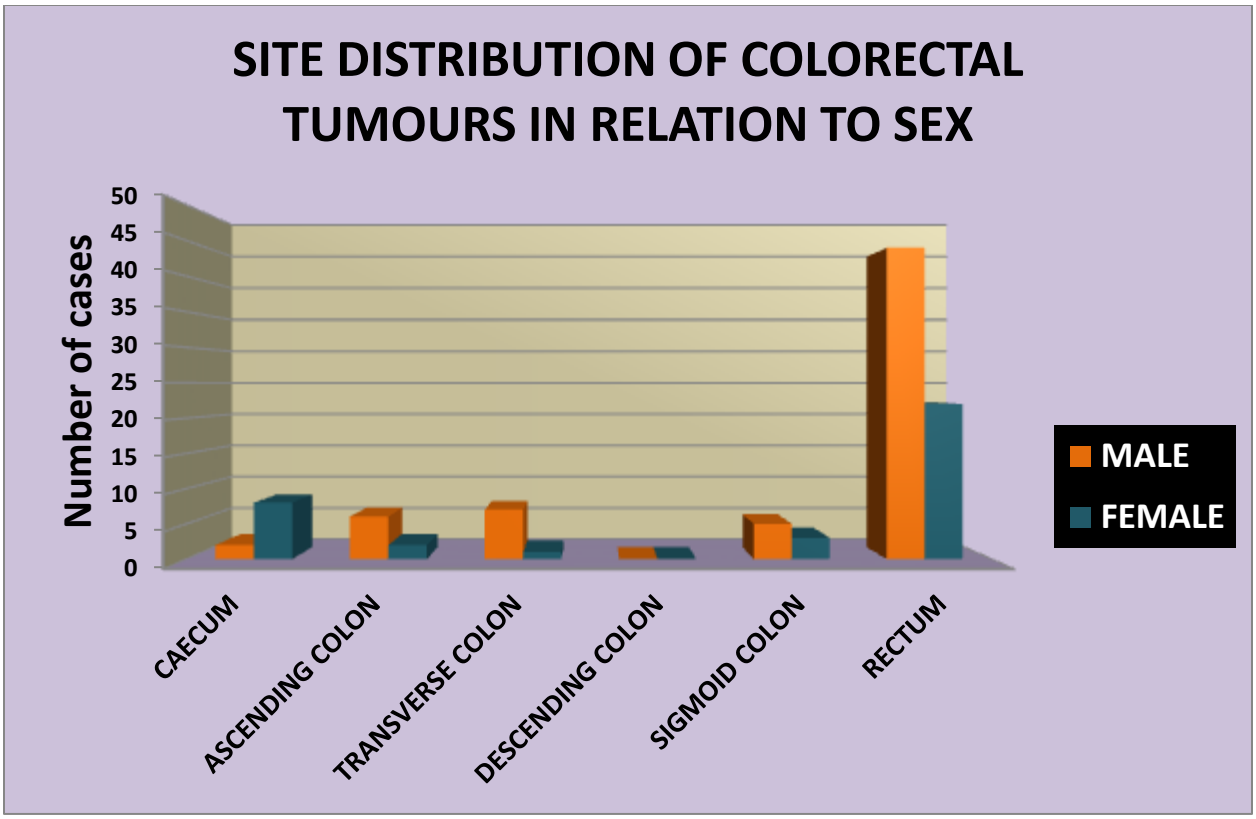

SITE DISTRIBUTION OF COLORECTAL TUMOURS IN RELATION TO SEX
Number of cases
50
45
40
35
30
25
20
15
10
5
0
CAECUM
ASCENDING COLON
TRANSVERSE COLON
DESCENDING COLON
SIGMOID COLON
RECTUM
MALE
FEMALE

CHART: 9

TABLE – 13

SITE DISTRIBUTION OF COLORECTAL TUMOURS IN RELATION TO AGE

AGE (Yrs)	SITE					
	CAECUM	ASCENDING COLON	TRANSVERSE COLON	DESCENDING COLON	SIGMOID COLON	RECTUM
10-20	0	0	1	0	0	0
21-30	0	1	0	0	1	1
31-40	1	3	2	0	1	12
41-50	2	2	1	0	3	20
51-60	3	0	3	0	2	17
61-70	4	2	0	0	0	14
71-80	0	0	1	0	1	2
TOTAL	10	8	8	0	8	66

From Table 13 (Chart 10), it is inferred that rectum was the most common site of malignancy in all age groups. Majority of tumours were seen in the age range of 40 – 60 years.

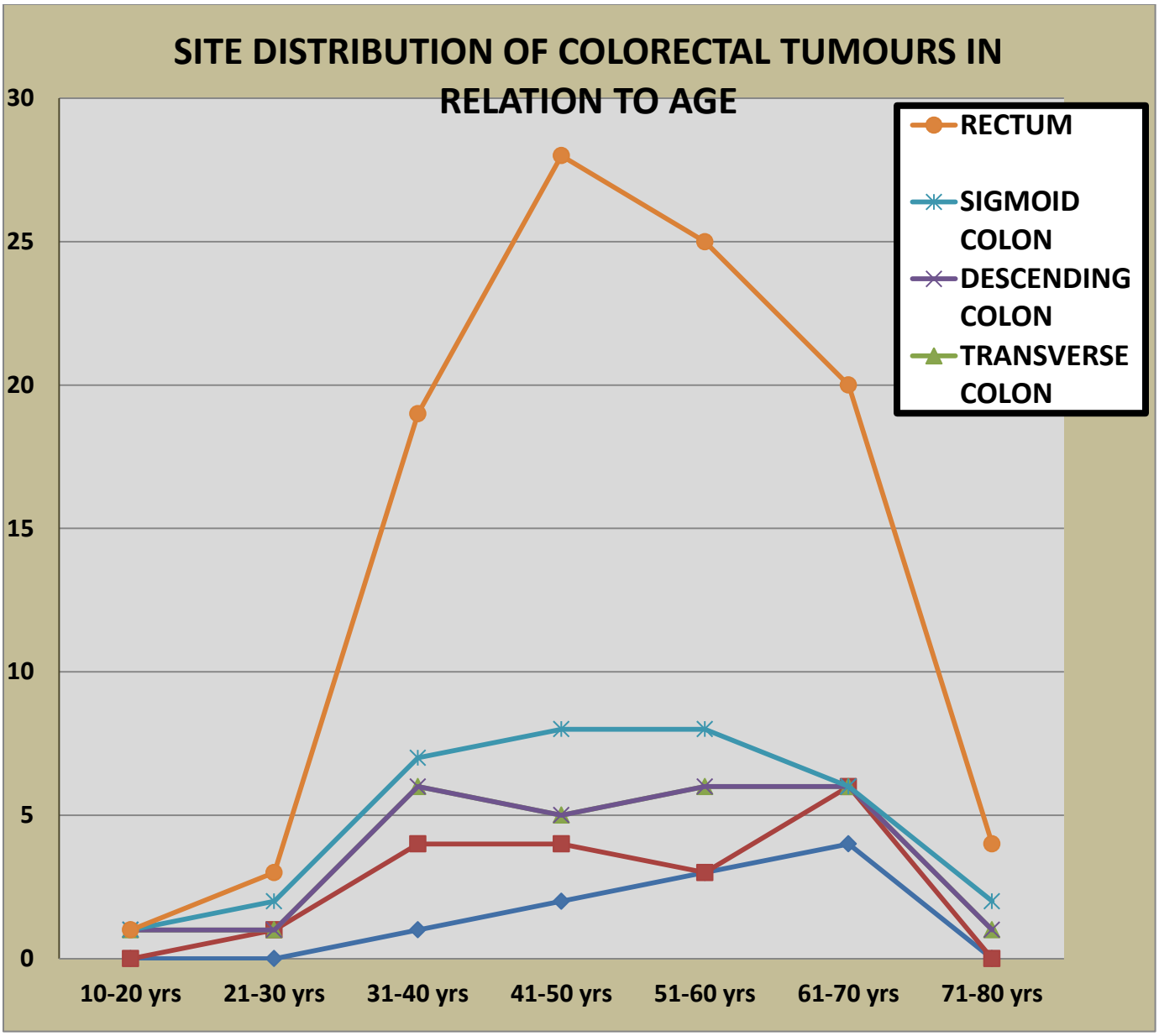

SITE DISTRIBUTION OF COLORECTAL TUMOURS IN RELATION TO AGE
30
25
20
15
10
5
0
10-20 yrs
21-30 yrs
31-40 yrs
41-50 yrs
51-60 yrs
61-70 yrs
71-80 yrs
RECTUM
SIGMOID COLON
DESCENDING COLON
TRANSVERSE COLON

CHART: 10

TABLE – 14

PATHOLOGICAL TYPES OF COLORECTAL TUMOURS

TUMOUR TYPE	NO OF CASES	%
ADENOCARCINOMA	82	82
MUCINOUS CARCINOMA	9	9
SIGNET RING CELL CARCINOMA	1	1
NEUROENDOCRINE CARCINOMA	1	1
MELANOMA	1	1
ADENOSQUAMOUS CARCINOMA	1	1

From Table 14 (Chart 11), it is inferred that adenocarcinoma is the most common histological type of colorectal tumours accounting for about 86% followed by mucinous adenocarcinoma (10%).

PATHOLOGICAL TYPES OF COLORECTAL TUMOURS

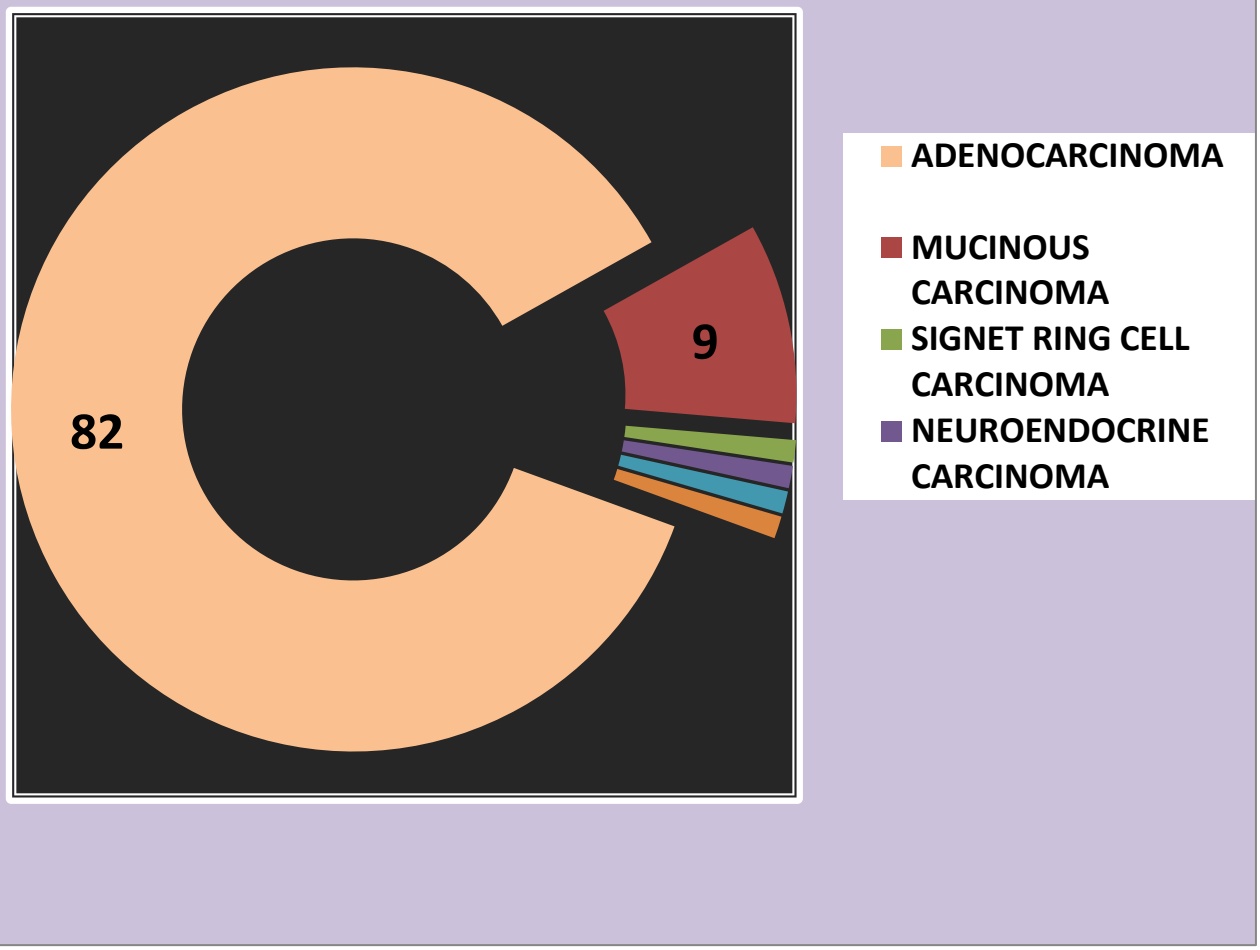


CHART: 11

TABLE – 15

HISTOLOGICAL GRADES OF COLORECTAL ADENOCARCINOMA

GRADE	NO. OF CASES	%
GRADE I	39	44
GRADE II	36	40
GRADE III	5	6
MUCINOUS CARCINOMA	9	10
TOTAL	89	100

Table 15 (Chart 12) shows well differentiated adenocarcinomas (Grade I) is the most common histological grade, followed by the moderately differentiated adenocarcinomas (Grade II).

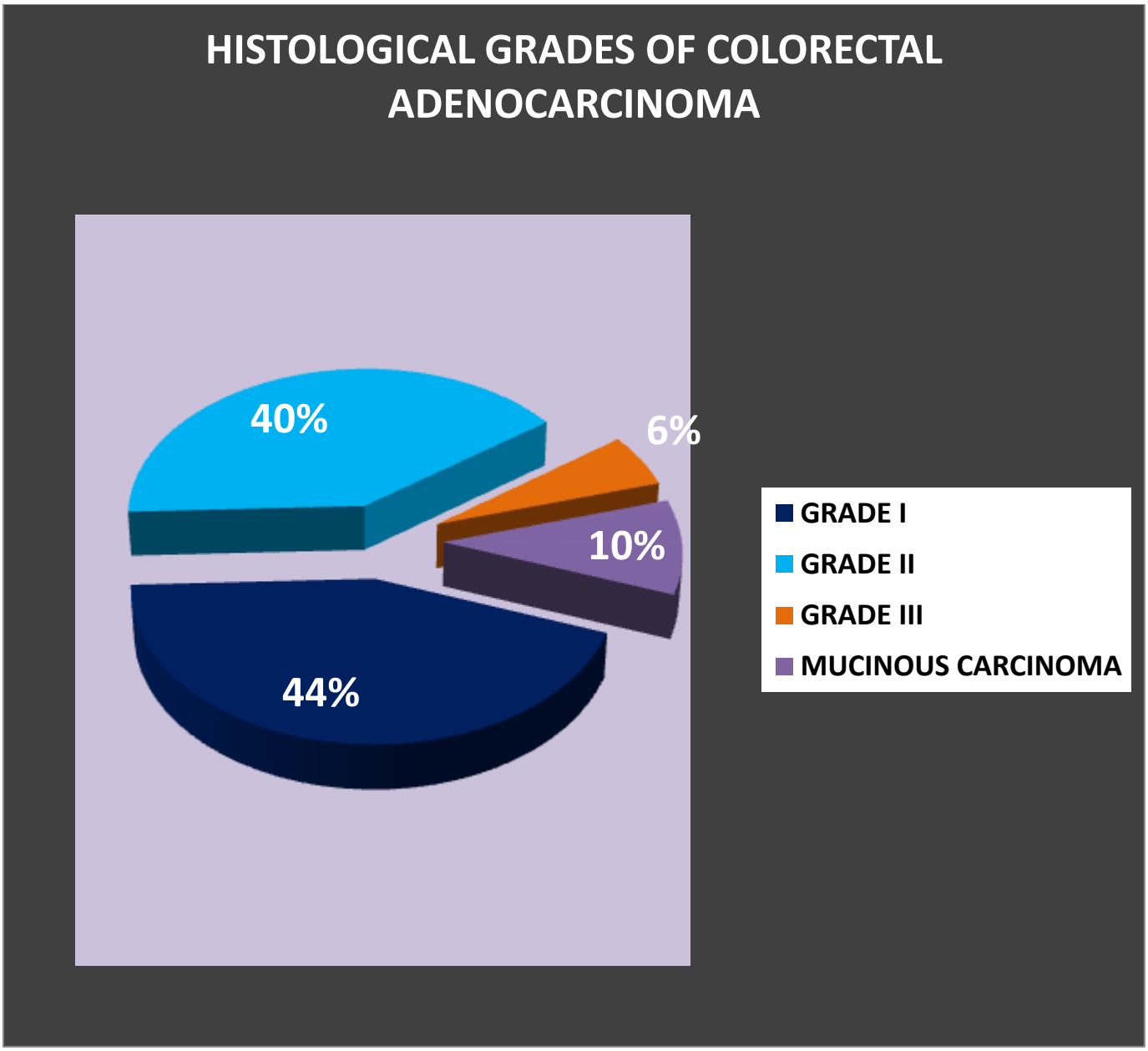

HISTOLOGICAL GRADES OF COLORECTAL ADENOCARCINOMA
40%
6%
10%
44%
GRADE I
GRADE II
GRADE III
MUCINOUS CARCINOMA

CHART: 12

TABLE – 16

AGE AND SEX DISTRIBUTION IN RELATION TO HISTOLOGICAL GRADES

AGE	GRADE I			GRADE II			GRADE III			MUCINOUS CARCINOMA			TOTAL		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
10-20	0	0	0	0	0	0	0	0	0	1	0	1	1	0	1
21-30	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1
31-40	7	1	8	2	2	4	2	0	2	1	3	4	12	6	18
41-50	4	7	11	5	5	10	2	0	2	2	0	2	13	12	25
51-60	10	4	14	7	1	8	1	0	1	1	0	1	19	5	24
61-70	4	1	5	7	4	11	0	0	0	0	1	1	11	6	17
71-80	1	0	1	2	0	2	0	0	0	0	0	0	3	0	3
TOTAL	26	13	39	23	13	36	5	0	5	5	4	9	59	30	89

Table 16 (Chart 13) shows all the histological grades showing male predominance and majority in the age range of 40 – 60 years.

AGE AND SEX DISTRIBUTION IN RELATION TO HISTOLOGICAL GRADES

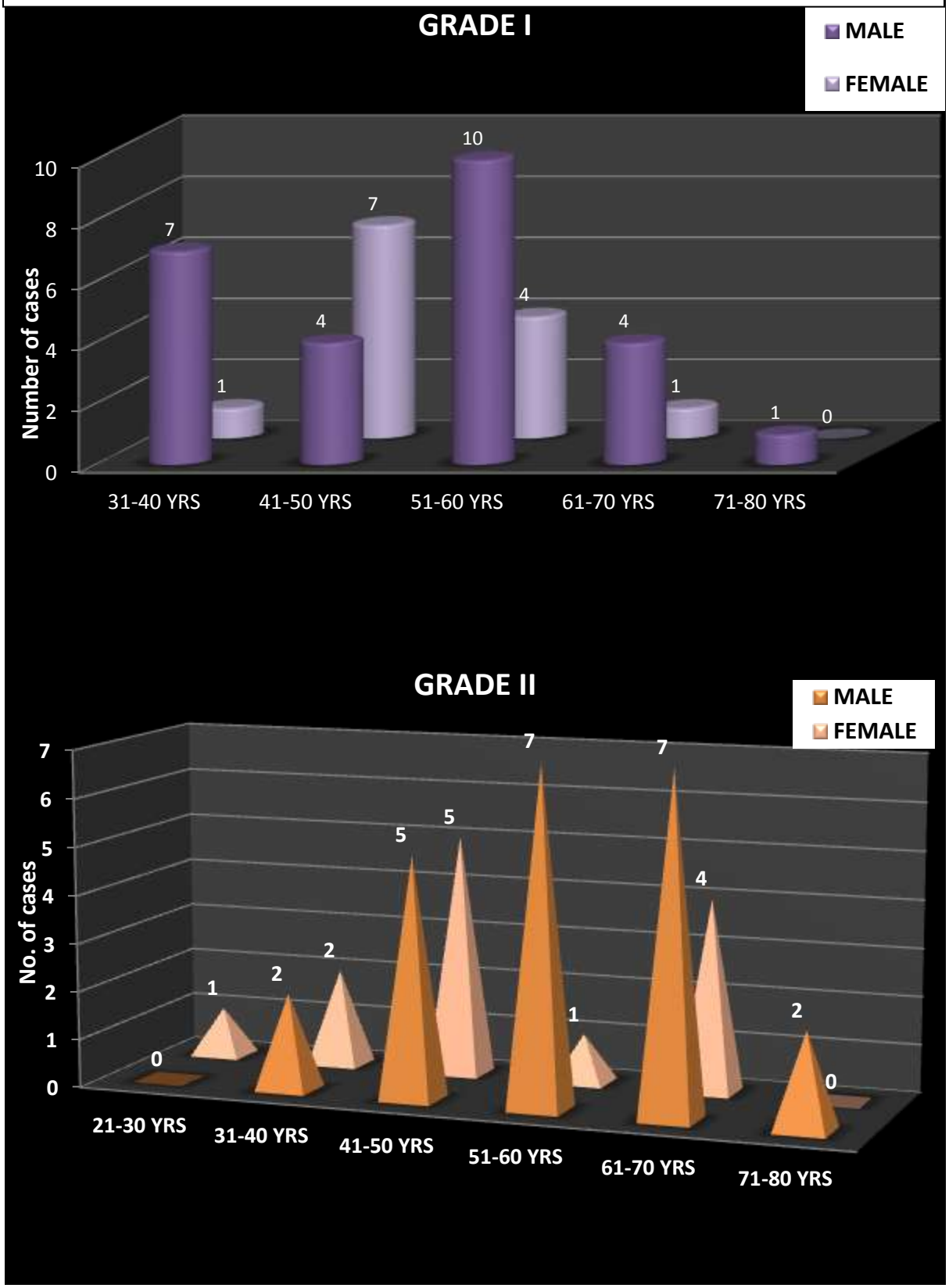


CHART: 13

TABLE – 17

STAGE DISTRIBUTION IN COLORECTAL ADENOCARCINOMA

STAGE	NO OF CASES	%
I	8	26
II	7	22
III	12	39
IV	4	13
TOTAL	31	-

From our statistical data, it is inferred that, stage III colorectal adenocarcinoma was more frequent (39%) than other stages (Table 17).

TABLE – 18

AGE AND SEX DISTRIBUTION IN RELATION TO STAGE

AGE	STAGE I			STAGE II			STAGE III			STAGE IV		
	M	F	T	M	F	T	M	F	T	M	F	T
10-20	0	0	0	0	0	0	1	0	1	0	0	0
21-30	0	0	0	0	1	1	0	0	0	0	0	0
31-40	1	0	1	1	1	2	1	0	1	2	0	2
41-50	0	0	0	1	2	3	1	2	3	1	0	1
51-60	4	1	5	0	0	0	2	1	3	1	0	1
61-70	1	1	2	0	1	1	3	1	4	0	0	0
TOTAL	6	2	8	2	5	7	8	4	12	4	0	4

Stage I & II tumours were categorized as low stage & Stage III & IV were categorized as high stage (Table 18) (Chart 14). In this study, low stage tumours predominated in both sexes and the high stage tumours were common in males.

AGE AND SEX DISTRIBUTION OF COLORECTAL TUMOURS IN RELATION TO STAGE

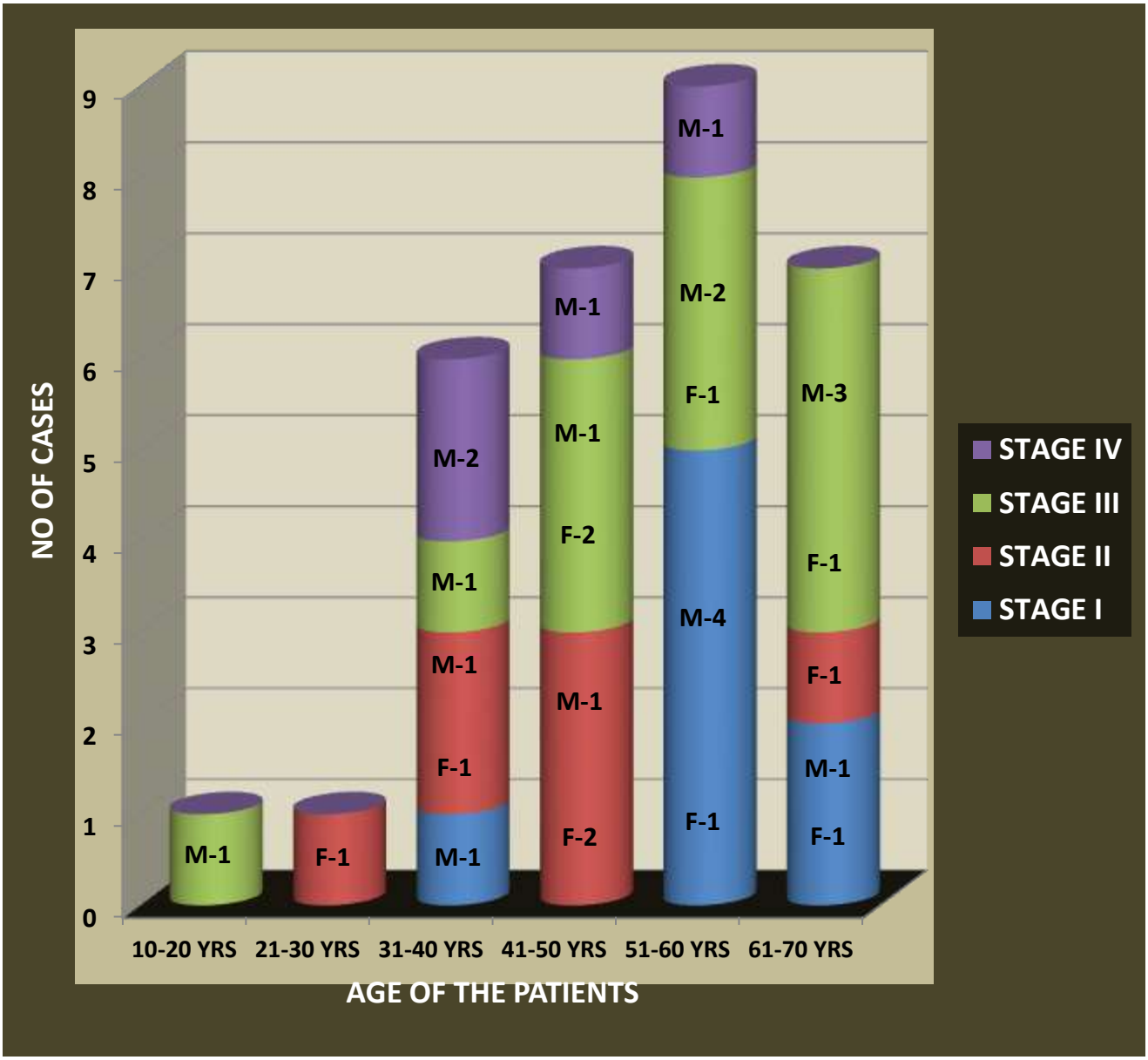


CHART: 14

TABLE – 19

p53 EXPRESSION IN COLORECTAL ADENOCARCINOMA

S.NO	HPE NO.	GRADE	STAGE	p53
1	3209/10	II	IV	+
2	3333/10	I	III	+
3	3460/10	I	III	+
4	3484/10	II	I	-
5	4044/10	I	I	-
6	4192/10	II	III	+
7	218/11	II	III	+
8	364/11	I	II	-
9	862/11	II	III	+
10	1236/11	II	II	-
11	1250/11	I	IV	+
12	1645/11	I	I	+
13	1689/11	Mucinous adenocarcinoma	II	-
14	2037/11	III	IV	+
15	2124/11	II	I	-

S.NO	HPE NO.	GRADE	STAGE	p53
16	2937/11	I	I	-
17	3101/11	I	III	-
18	3384/11	I	IV	-
19	3461/11	II	II	+
20	4073/11	Mucinous adenocarcinoma	II	-
21	4227/11	Mucinous adenocarcinoma	III	-
22	4289/11	II	II	+
23	519/12	II	III	+
24	610/12	I	I	-
25	722/12	II	II	-
26	1027/12	Mucinous adenocarcinoma	III	+
27	1189/12	I	I	+
28	1522/12	II	III	+
29	1992/12	II	III	-
30	2120/12	II	III	+

TABLE – 20

p53 EXPRESSION IN COLORECTAL ADENOCARCINOMA

ADENOCARCINOMA	p53				TOTAL
	+	%	-	%	
CONVENTIONAL ADENOCARCINOMA	15	57.7	11	42.3	26
MUCINOUS ADENOCARCINOMA	1	25	3	75	4
TOTAL	16	53.3	14	46.7	30

In this study 53.3% of the colorectal adenocarcinomas showed p53 positivity. p53 over expression was more frequent in non-mucinous adenocarcinomas than in mucinous adenocarcinomas (Table 20).

TABLE – 21

p53 EXPRESSION IN COLORECTAL ADENOCARCINOMAS IN RELATION TO STAGE

STAGE	p53		TOTAL	POSITIVE CASES %
	+	-		
I	2	5	7	28.57
II	2	5	7	28.57
III	9	3	12	75
IV	3	1	4	75
TOTAL	16	14	30	-

For the purpose of statistical analysis stages I and II were considered as low stage tumours and stages III and IV were considered as high stage. The proportion of positively reacting colorectal tumours increases as the stage progresses. Statistical analysis using Chi- square test was done which revealed a P value of <0.05 (X^2 = 4.74) which is statistically significant. Hence p53 expression is significantly correlated with the stage of tumour in colorectal adenocarcinoma (Table 21) (Chart 15).

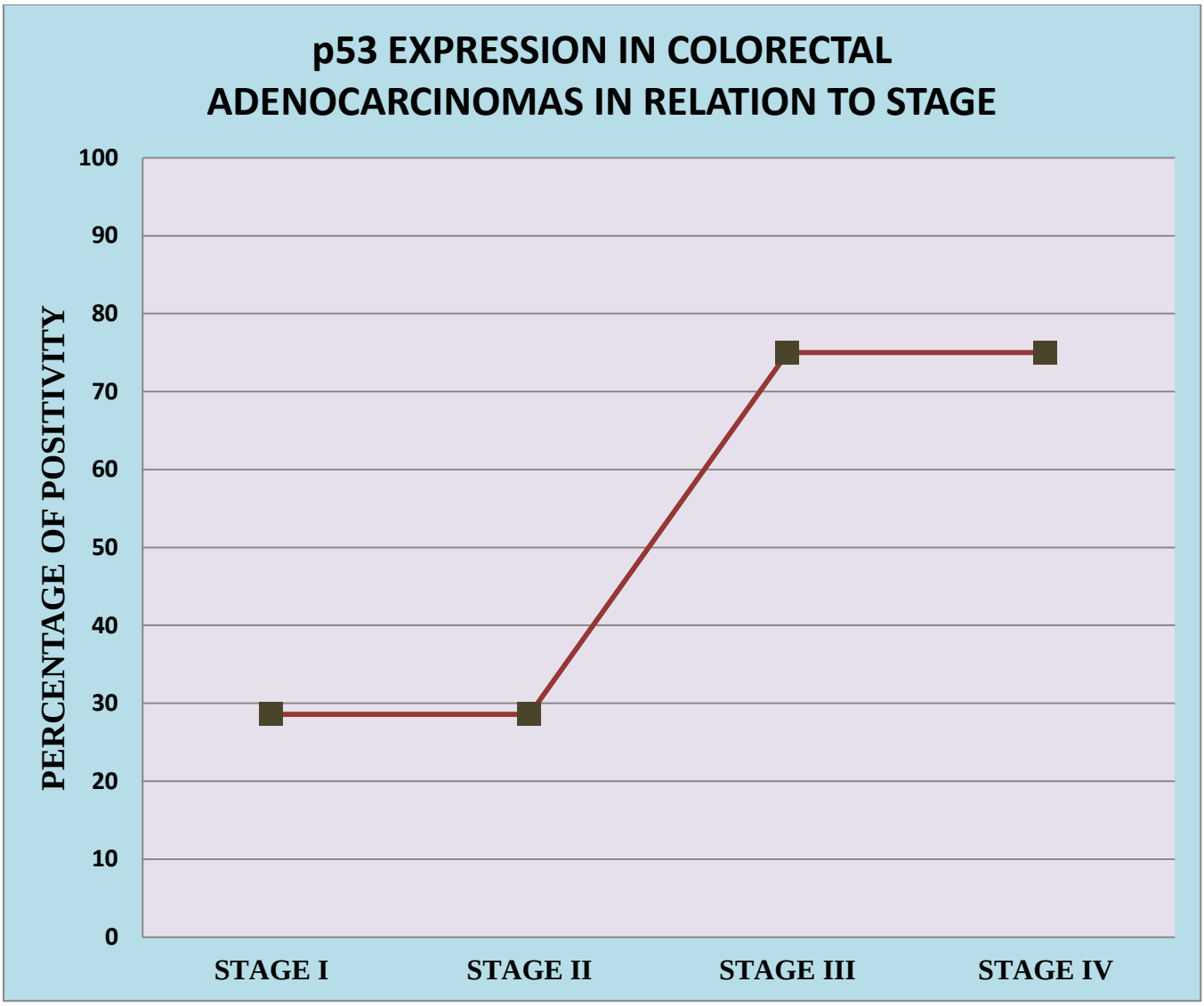

p53 EXPRESSION IN COLORECTAL ADENOCARCINOMAS IN RELATION TO STAGE
PERCENTAGE OF POSITIVITY
100
90
80
70
60
50
40
30
20
10
0
STAGE I
STAGE II
STAGE III
STAGE IV

CHART: 15

DISCUSSION

Tumours of intestines are some of the common neoplasms encountered and they demonstrate an array of histological patterns, varied clinical presentations, an assortment of gross patterns and an immense variability in their prognosis.

In our retrospective study, done during Jan2010 to June2012 at Thanjavur medical college and hospital, of 111 cases of intestinal neoplasms, 100 specimens were from large intestine and 11 specimens were from small intestine, the incidence is 2.6%. Of total malignancies large intestine constitutes 2.99% and small intestine 0.3%. This is in accordance with the study done by Ioannis Hatzaras et al.[36]

However in India, these tumours are relatively rare but its incidence is increasing and varies from place to place.

Colorectum is the leading site for cancer in developed countries and small bowel cancers are rare worldwide. The incidence rate of large bowel cancer in India is about 7 per 1lakh population and that of incidence rate of small bowel cancer is less than 1 per 1lakh population worldwide.[70] The incidence of both small and large bowel cancers are low in India.[53] The incidence of colorectal cancer in India is 3.6% when compared worldwide (10%).[34]

In our study of 111 cases 90% are large bowel tumours and small bowel tumours are only 10%. When compared to benign tumours (7%), malignant tumours (93%) are more common. Tumours of intestine were seen over a wide range of age group (18 – 75 yrs) with highest distribution in the 4^{th} to 6^{th} decade. This correlates with the study done by Abou Zeid AA et al[2] and T. Starzynska et al.[77].

SMALL BOWEL NEOPLASMS:

Small bowel tumours constitute only 1-2% of all gastrointestinal tumours. According to Sai Yi Pan et al[70], the incidence of small intestine cancer increasing over the past several decades with a four-fold increase for carcinoid tumours, less dramatic rise for adenocarcinoma and lymphoma and stable for sarcoma.

In the present study, the highest distribution of small intestinal neoplasms is commonly seen in the age group of 30-50 yrs and shows no sexual predominance.

In general, higher small intestinal cancer incidence rate have been described among males in north America, Europe, Asia and central / south America, with exceptions, noted in Iceland, Italy, Poland, Brazil, Australia and Japan, where incidence rate are higher among females. But the studies done by David Lewin et al[16] and Tadashi Terada et al[78] show a slight male predominance and an average age of presentation ranging from 55-63 yrs. This difference in the distribution of small intestinal neoplasms might be attributed to the number of cases studied.

The male predominance of small intestinal cancers is similar to that described for carcinomas at other primary sites, a pattern attributed, in part, to environmental, endogenous and behavioural factors that differ by gender.[62]

According to Osama Qubaiah et al[62], all histological subtypes of small intestine cancers predominated among men with distinct age specific pattern among males and females limited to lymphomas. Small intestine lymphomas are uniquely characterized by increased incidence in young males but not females.

Most common presentation of the small intestinal tumour is intestinal obstruction. This is in accordance with the study by David Lewin et al.[16]

In the present study duodenum is the most common site and the most common histological type is adenocarcinoma. In the ileum malignant lymphoma is the most common histological type which constitutes more than half of all malignancies and the fact correlates well with the study done by Zhou-Zhi-Wei et al[89] and Gill SS et al.[29]

In the present study, among 11 cases of small intestinal neoplasms, more than 2/3rd are malignant. The incidence of malignant tumours correlates with the study done by Ioannis Hatzaras et al.[36] Of small intestinal tumours 36% are adenocarcinoma, 36% of cases are lymphomas, 18% of cases are benign tumours and 9% are metastatic malignant melanoma deposit. This correlates with the study done by Zhou Zhi-Wei et al.[89]

According to David Lewin et al[16], benign tumours represent approximately 40% of small intestinal tumours. 30% are smooth muscle stromal tumours, 20% are adenomas and 15% are lipomas. Of malignant tumours 33% are adenocarcinoma, 33% are carcinoids, 20% are lymphomas and 10% are mesenchymal origin. Another study done by Zhou Zhi-Wei et al[89] adenocarcinoma is the most common tumour followed by malignant lymphoma.

In our study, we received a small intestine specimen with secondary malignant melanoma deposits, primary was from the sole, which is a rare occurrence. According to Washington K et al[83], metastatic tumours can involve small bowel often in the form of multiple polypoid tumours and may result in obstruction or perforation, necessitating palliative resuscitation. The most common type of primary tumours is malignant melanoma, carcinoma from lung, breast, ovary and choriocarcinoma. Patients with multiple metastases of melanoma usually die within 1 year following palliative surgery. But an occasional long term survival will be found among those with isolated metastasis.[86]

LARGE BOWEL NEOPLASMS:

Large bowel cancer is an important public health problem. Each year there are nearly one million new cases of colorectal cancer diagnosed worldwide. Colorectal cancer related deaths account for more than half a million. According to Peter Boyle et al in the United states, colorectal cancer was the most common malignancy among persons aged 75 years and older.[64]

Racial and ethnic differences in colon cancer and studies on migrants suggest that environmental factors play a key role in the development of the disease.

The development of large bowel cancer is a multistep process involving genetic mutations in mucosal cells, the activation of tumour promoting genes and the loss of genes which suppress tumour formation.[82]

Most of the colorectal carcinomas arise from benign adenomatous polyps which grow a large size. Those that have villous appearance or contain dysplastic cells are most likely to progress to cancer.[66]

Individuals with risk factors namely FAP syndromes and inflammatory bowel diseases have high risk of developing colorectal tumours but it constitute only a small proportion of the overall incidence.[12,48]

According to Langmann et al, chemopreventive drugs for colorectal carcinomas include vitamin A or β carotene, vitamin E, vitamin D, folate, H2 antagonist, anti-inflammatory drugs and calcium supplements.[42]

Peak incidence of colorectal cancer is 60-79 years. Fewer than 20% of cases occur before the age of 50 years.[9] According to Peter Boyle et al,[64] global age standardized rates of colorectal carcinoma incidence are higher in men than in women. The risk of colorectal cancer rises significantly after the age of 40 years in both men and women and doubles in each succeeding decade until the age of 75. The median age at diagnosis is 71 years of age.[24] In North America and Australia (areas with high rates of colorectal cancer) and in Japan and Italy (countries with rapidly raising rates), the age adjusted incidence of colorectal cancer for men exceeds women. With lesions in the rectum male: female is 1.2:1. For more proximal tumours there is no gender difference.

In our study, age group range from 20-75 years (Mean age – 51.4 years). Male predominance was seen in all colorectal carcinomas. This is in accordance with the study done by Abou Zeid AA et al[2] and T. Starzynska et al.[77] (Table 22)

TABLE – 22

S.NO	STUDIES	AGE RANGE (yrs)	MEAN AGE (yrs)
1	Abou-zeid et al[2]	19 – 74	46
2	T. Starzynska et al[77]	22 – 80	65.4
3	Yuan-Tzu Lan et al[87]	18 – 92	66.9
4	George E. Theodoropoulos et al[28]	45 – 82	63.5
5	Present study	20 – 75	51.4

Majority of colonic tumours are seen in the sigmoid colon and the rectum. In recent years there is evidence of increasing proportion of proximal tumours. In high risk countries colorectal cancer most commonly arises in the recto-sigmoid region, but though we fall in the low risk countries we encountered more lesions in the distal region may be due to environmental factors or easy approachability which made them to be detected at an early stage as many of these are well differentiated adenocarcinomas. [48]

TABLE – 23

LOCATION OF COLORECTAL CARCINOMA IN DIFFERENT STUDIES AS PERCENTAGE					
S.NO	**SITE**	**Abdul Kareem FB et al (2008)**[1] **(%)**	**Osime U et al (1988)**[63] **(%)**	**Qizilbash AH (1982)**[68] **(%)**	**Present study (%)**
1.	Caecum	9	2.63	13.53	10
2.	Ascending colon	6	2.63	11.28	8
3.	Hepatic flexure	0	1.32	1.50	--
4.	Transverse colon	4.5	1.32	4.89	8
5.	Splenic flexure	0	1.32	2.63	--
6.	Descending colon	3.6	3.94	6.77	--
7.	Sigmoid colon	0	7.89	34.21	8
8.	Recto sigmoid	58.8	--	9.02	--
9.	Rectum	--	78.95	14.28	66
Total number of cases		420	76	266	100

In the present study 74 of the 100 colorectal tumours were located in the left side (sites being rectum, sigmoid, descending colon and splenic flexure). Most common site was rectum with 66% of cases. This is in accordance with the study by Osime U et al.[63] (Table 23)

In the present study bleeding per rectum was the most common clinical presentation (55%) of the colorectal tumours.(Table 9)

According to Chen Liu et al, tumours of the caecum and ascending colon tend to grow as polypoid exophytic masses. Distal colon carcinomas are annular lesions that produce so called 'napkin ring' constriction of the bowel.[9]

TABLE – 24

GROWTH PATTERNS OF COLORECTAL ADENOCARCINOMA					
S.NO	**STUDIES**	**ULCEROPROLIFERATIVE (%)**	**POLYP (%)**	**NARROWING OF LUMEN (%)**	**TOTAL**
1.	Qizilbash AH (1982)[68]	54	28	18	100
2.	Present study	82	10	8	100

But most of the tumours in the present study (82%) were ulceroproliferative growth in both proximal and distal colon (Table 10). This correlates with the study done by Qizilbash AH.[68] (Table 24)

In our study of 100 colorectal tumours 95 cases were malignant, remaining 5 cases were benign, of which 91% were adenocarcinomas. Signet ring cell carcinoma, neuroendocrine carcinoma, adenosquamous carcinoma, melanoma contributes to 1% each.

TABLE – 25

INCIDENCE OF DIFFERENT TYPES OF MALIGNANT TUMOURS OF COLON						
S.NO	**STUDIES**	**ADENOCARCINOMAS**		**OTHERS**		**TOTAL**
		No. of cases	**(%)**	**No. of cases**	**(%)**	
1.	Abdul Kareem FB et al (2008)[1]	405	96.4%	15	3.6%	420
2.	Osime U et al (1988)[63]	73	96.05%	3	3.95%	76
3.	Qizilbash AH (1982)[68]	244	94.9%	13	5.1%	257
4.	Present study	91	91%	4	4%	100

In the present study adenocarcinoma was the most common type of malignancy encountered in the colon accounting for 91% of the tumours (Table 14), a finding that correlates with the study done by various authors. (Table 25)

Mucinous tumours are less common and accounts for 10 – 15% of colorectal carcinomas.

TABLE – 26

INCIDENCE OF MUCINOUS AND NON MUCINOUS ADEENOCARCINOMA						
S.NO	**STUDIES**	**MUCINOUS ADENO CARCINOMA**		**NON MUCINOUS ADENOCARCINOMA**		**TOTAL**
		No. of cases	**(%)**	**No. of cases**	**(%)**	
1.	Qizilbash AH (1982)[68]	14	5	244	91.78	266
2.	Osime U et al (1988)[63]	4	5.26	69	90.79	76
3.	Fazeli MS et al (2007)[23]	71	17.6	332	82.4	403
4.	Abdul Kareem FB et al (2008)[1]	45	10.7	360	89.3	405
5.	Present study	9	9	81	81	100

In the presemt study mucinous adenocarcinoma constitute about 9%, a finding similar to study done by Abdul Kareem FB et al.[1] however the findings varied in different studies. (Table 26)

Mucinous adenocarcinomas were located in the right side of the colon and rectum. It shows a male predominance and mucinous adenocarcinoma patients

were younger than adenocarcinoma patients. This is in accordance with the study done by J Verhulst et al[37] and Azadeh Safaee et al.[5]

Mucinous adenocarcinoma showed a higher proportion of high grade tumours. The adverse prognostic effect of mucinous adenocarcinoma can be explained by more advanced stage at presentation. Mucin content when considered together with histological grade can be regarded as important prognostic indicators.[56] MUC1/DF3 and MUC5/CHL2 immunostaining is useful to distinguish between low grade and high grade mucinous adenocarcinoma. MUC2 and MUC5AC expression may be particularly helpful in predicting the clinical outcome of this type.[57]

TABLE - 27

HISTOLOGICAL GRADE OF ADENOCARCINOMA IN VARIOUS STUDIES								
S.NO	**STUDIES**	**GRADE I**		**GRADE II**		**GRADE III**		**TOTAL**
		NO. of cases	**(%)**	**NO. of cases**	**(%)**	**NO. of cases**	**(%)**	
1.	Abdul Kareem et al (2008)[1]	233	65.6	88	24.7	34	9.5	355
2.	Fazeli MS et al (2007)[23]	133	37.6	187	52.8	34	9.6	354
3.	Osime V et al (1988)[63]	7	10.14	40	57.97	22	31.88	69
4.	Present study	39	44	36	40	5	6	89

The present study shows higher incidence of well differentiated adenocarcinoma, which correlates with the study done by Abdul Kareem FB et al.[1] (Table 27) However the findings varied in different studies.

TNM STAGING:

Pathological TNM staging was carried out for 31 resected specimens in the present study.

TABLE – 28

TNM STAGING OF ADENOCARCINOMA IN DIFFERENT STUDIES									
S.NO	**STAGE**	**Abdul Kareem FB et al (2008)**[1]		**Fazeli MS et al (2007)**[23]		**Yuan-Tzu Lan et al**[87]		**Present study**	
		No. of cases	**(%)**	**No. of cases**	**(%)**	**No. of cases**	**(%)**	**No. of cases**	**(%)**
1.	I	17	14	33	8.2	41	15.9	8	26
2.	II	64	51	193	48.1	83	32.2	7	22
3.	III	41	34	134	33.04	85	32.9	12	39
4.	IV	1	1	41	10.2	49	19	4	13
TOTAL		123		401		258		31	

In the present study stage III was more frequent(39%). This is in accordance with the study by Yuan-Tzu Lan et al.[87] (Table 28)

p53 IMMUNOEXPRESSION – SMALL INTESTINE:

p53 expression was studied in 5 small intestinal tumours of which 3 cases were adenocarcinoma and 2 cases were lymphomas. p53 expression was quantified according to DA Spandidios et al[15] and results were tabulated and analysed. In the present study p53 expression is seen in 60% of small intestinal tumours. Of 3 cases of adenocarcinoma 2 cases (67%) were p53 positive and 1 out of 2 cases (50%) of lymphoma were positive for p53. Intense positivity were seen in lymphomas (>50% of cells). This is in accordance with the study done by DA Spandidos et al.[15]

DA Spandidos et al[15] found immunoreactivity in 46% of small intestinal tumours. Ge C, He S, Tian Y[27] reported nuclear positivity for p53 in 75% of small intestinal tumours. Tadashi Terada [78] found 51.21% of p53 positivity in small intestinal tumours. M Svrcek et al[44] found p53 positivity in 51.85% of small intestinal adenocarcinoma. Krugmann et al[41] reported p53 overexpression in 75% of small intestinal lymphomas. These differences may be due to the use of different scoring system and inter-observer variability.

D A Spandidos et al[15] concluded that p53 gene may be involved in the pathogenesis of small intestinal tumours. Tadashi Terada,[78] in his study, found that p53 protein overexpression was present in most of the primary small intestinal carcinomas. Ge C et al[27] in their study showed that the degree of p53 protein

expression was significantly correlating with the grade of the tumour cell differentiation, invasion, metastasis and prognosis. According to Krugmann et al[41] and Ming Qing et al[50] p53 overexpression in small intestinal lymphomas is a critical factor in the transformation of low grade MALT lymphoma and the overexpression also indicate the aggressive behavior of high grade tumours.

p53 immunoexpression was seen in both small intestinal adenocarcinoma and lymphoma. Intense positivity was observed in small intestinal lymphoma. This shows the involvement of p53 gene in the pathogenesis of small intestinal tumours. Due to low sample size, the prognostic value of p53 could not be determined.

p53 IMMUNOEXPRESSION IN COLORECTAL TUMOURS:

p53 tumour suppressor gene is one of the most intensively studied tumour markers in the colorectal tumours. In this study 30 cases of colorectal carcinoma (colectomy specimens) were selected for the study of p53 expression by immunohistochemistry in various stages which included 4 mucinous adenocarcinomas. For the purpose of statistical analysis stages I and II were categorized as low stage and stages III and IV were categorized as high stage. According to George E Theodoropoulous et al[28] p53 immunostaining was done and the results were tabulated and analysed.

TABLE – 29

S.NO	STUDIES	p53 EXPRESSION (%)
1.	Mohammad – Reza et al[51]	59
2.	T Starzynska et al[77]	46
3.	Scott N et al[72]	42
4.	O Petrisor et al[60]	66
5.	George E Theodoropoulous et al[28]	63.4
6.	Present study	53.3

In our study 53.3% of colorectal adenocarcinoms showed p53 nuclear protein overexpression. These differences may be due to the use of different scoring system and inter-observer variability. (Table 29)

In the present study p53 expression was more frequent in non-mucinous adenocarcinomas (57.7% Vs 25%). (Table 20) This is in accordance with the study by Yuan-Tzu-Lan et al[87] who found that 39% of non-mucinous adenocarcinomas and 29% of mucinous adenocarcinomas showed p53 positivity and suggesting two different pathways, chromosomal instability and microsatellite instability of colorectal carcinogenesis respectively. T Starzynska et al[77] studied the relation of p53 expression in colorectal carcinoma with histological, clinical, prognostic features using follow-up data and concluded that p53 expression occurred as a late event and was associated significantly associated with advanced stage of disease,

early relapse and death. J Walker et al[38] in their study found that the stage is the most accurate prognostic factor for survival. They concluded that p53 overexpression in colorectal carcinoma correlated with poor prognosis. In this study the proportion of p53 nuclear protein expression increases as the stage progresses. This association was proved to be statistically significant by using chi square test ($P < 0.05$). This is in accordance with the study done by T Starzynska et al,[77] George E Theodoropoulous et al.[28] Several previously published series have supported the deleterious effect of p53 over expression.[26,30,6]

Vikos et al studied 41 colorectal tumours showed a significant association between elevated p53 and the presence of DNA aneuploidy, a factor that correlated with poor prognosis. They also suggested the fact that evaluating p53 expression may prove helpful in determining various biological subgroups of colorectal carcinomas. Scott N et al[72] analysed 52 colorectal carcinomas in their study and found no correlation with p53 overexpression and several factors related to prognosis.

Campo et al (1991)[7] also, did not find relationship between p53 expression and degree of differentiation and stage of the tumour, concluded that p53 is not a good prognostic indicator in large bowel malignancy. The discrepancies in the prognostic role of p53 in colorectal adenocarcinomas might be a result of different

kind of materials, methods and antibodies used or differences in the number of tumours examined.

p53 expression increases as the stage progresses, stage is the established prognostic factor in colorectal carcinoma, and also there is significant correlation between high p53 levels and stage of the colorectal carcinomas, so it can be used as a prognostic marker to asses invasiveness and metastatic potential of the colorectal tumours.

SUMMARY AND CONCLUSION

- This is a retrospective study undertaken in the department of pathology over a period of jan 2010 to june 2012.
- Resected specimens and biopsies of intestinal tumours were included for the study.
- The number of specimen included for the study were 111, 100 from large intestine and 11 from small intestine, of which biopsy specimens were 74(66.67%) and resected specimens were 37(33.33%).
- Age, sex and site of the lesion were recorded.
- Incidence of intestinal neoplasms was 2.6% of the total neoplasms in our institution.
- Grading and staging of colorectal carcinomas were done.
- Immunohistochemistry using p53 antibody was done to assess the role of its expression in various types of intestinal tumours. Results were tabulated and analysed.

Small intestinal tumours:

- Incidence of small intestinal cancer – 0.3%.
- Age group range from 18 – 70 years with peak incidence in 30 – 50 years.

- Most common clinical presentation of small intestinal neoplasm is intestinal obstruction (73%).
- Most of the small bowel neoplasms arise from the duodenum (64%).
- Of the small intestinal tumours adenocarcinoma and lymphomas have equal incidence.
- p53 gene is involved in the pathogenesis of small intestinal tumours.

Colorectal tumours:

- Incidence of colorectal cancer – 2.99%
- Age group range from 20 – 75 years with peak incidence in 40 – 60 years.
- Bleeding per rectum is the most common clinical presentation (55%).
- Most of the colorectal cancer grossly present as ulceroproliferative lesion (82%).
- Rectum is the most common site of occurance (66%) in both sexes.
- Most of the colorectal tumours show male predominance.
- Adenocarcinoma is the most common histological type of colorectal tumours (80%) followed by mucinous adenocarcinoma (9%).
- Most of the colorectal adenocarcinoma are well differentiated type.
- Stag III colorectal adenocarcinoma is more frequent (39%) than other stage.
- The low stage tumours predominated in both sexes and the high stage tumours are common in males.

p53:

In colorectal tumours p53 expression increases as the stage progresses and also there is significant correlation between high p53 levels and stage of colorectal carcinomas. So it can be used as a prognostic marker to assess invasiveness and metastatic potential of the colorectal tumours.

There is a statistically significant correlation between p53 protein expression and stage of the colorectal cancer and hence p53 immunoreactivity is an important independent prognostic marker in patients with colorectal carcinoma. P53 protein overexpression has been associated with a worst overall survival after cancer diagnosis. Considering the acceptable reliability and feasibility of detection of p53 by immunohistochemistry, this marker may be expected to serve as a new genetic marker for predicting recurrence and response to chemotherapy in patients with colorectal cancer.

APPENDIX

APPENDIX – I

HAEMATOXYLIN AND EOSIN STAIN

PREPARATION OF SOLUTIONS:

HARRIS HAEMATOXYLIN

Distilled water - 1000ml

Ammonium alum - 100g

Haematoxylin - 5g

Absolute ethyl alcohol - 50ml

Mercuric oxide - 2.5g

100g of ammonium alum is dissolved in 1000ml of distilled water by heating and shaking at 60ºC. Add solution of 5g of haematoxylin in 50ml of ethyl alcohol and bring rapidly to boil. When it begins to boil, remove from flame and add 2.5g of mercuric oxide. Mix by swirling gently.

EOSIN STAIN

Eosin Y - 1g

Distilled water - 100ml

Dissolve 1g of eosin in 100ml of water.

PROCEDURE:

1. Dewax the sections through 2 changes of xylene and hydrate the sections through descending grades of alcohols to water.
2. Stain in Harris Haematoxylin for 5 minutes.
3. Quickly rinse in running water.
4. Differentiate in 1% acid alcohol (2-3 dips).
5. Blue the sections in running tap water for 10 minutes.
6. Stain in 1% aqueous Eosin Y for 30 seconds.
7. Dehydrate, clear and mount.

APPENDIX – II

IMMUNOHISTOCHEMISTRY

1. 4 micron thick sections were cut from the formalin fixed, paraffin embedded tissue sections on slides coated with chrome alum gelatin.
2. Dewax sections through 2 changes of xylene and hydrate the sections through descending grades of alcohol to water.
3. Slides are placed in antigen retrieval buffer solution (Tris EDTA / Citrate buffer) inside microwave oven at required temperature and time.
4. Wash in running tap water for 5 minutes.
5. Slides are immersed in hydrogen peroxide for 10 minutes to block endogenous peroxidase activity.
6. Wash in Tris buffer solution for 5 minutes.
7. Slides are placed in power block reagent for 10 minutes to block nonspecific reaction with other tissue antigens.
8. Slides are drained and covered with the concerned primary antibody for one hour.
9. Wash in Tris buffer solution for 5 minutes.
10. Slides are placed in super enhancer solution for 30 minutes to enhance the reaction between primary and secondary antibodies.

11. Wash in Tris buffer solution for 5 minutes.
12. Place in enzyme labeled polymer secondary antibody (super sensitive poly HRP) for 30 minutes.
13. Wash in Tris buffer solution for 5 minutes.
14. Diamino benzidine (DAB) was used as chromogen.
15. Wash in distilled water for 2-4 minutes.
16. Counter stained with Harris haematoxylin for 1 minute.
17. Cleared in xylene, mounted.

S.NO	BIOPSY NO	AGE	SEX	BPR	ALT BH	LOW	SITE	CONFIGURATION	HPE	GRADE	STAGE	p53
1	214/10	40	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA			
2	267/10	32	M	N	Y	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	NEUROENDOCRINE CARCINOMA			
3	495/10	30	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOSQUAMOUS CARCINOMA			
4	573/10	60	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
5	725/10	60	M	N	N	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
6	816/10	38	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
7	968/10	36	M	N	Y	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
8	1045/10	45	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
9	1179/10	73	M	N	Y	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
10	1281/10	65	M	Y	N	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	I		
11	1494/10	44	M	Y	N	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA			
12	1670/10	58	M	N	Y	N	SIGMOID COLON	NARROWING OF LUMEN	ADENOCARCINOMA	I		
13	1791/10	56	M	Y	N	N	RECTUM	POLYP	ADENOCARCINOMA	I		
14	1917/10	45	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
15	2155/10	46	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
16	2267/10	73	M	Y	N	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	I		
17	2323/10	60	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
18	2453/10	39	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
19	2548/10	51	F	Y	N	N	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
20	2641/10	40	F	N	Y	N	CAECUM	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA			
21	2689/10	39	M	N	Y	N	RECTUM	POLYP	ADENOCARCINOMA	I		
22	2751/10	48	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
23	2782/10	65	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
24	2783/10	37	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
25	2807/10	44	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	III		
26	2969/10	71	M	Y	N	Y	SIGMOID COLON	POLYP	ADENOCARCINOMA	II		
27	3020/10	58	M	Y	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
28	3046/10	40	F	N	Y	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
29	3209/10	53	M	Y	N	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	IV ($T_4N_1M_1$) (M-Ovary)	+
30	3297/10	53	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
31	3333/10	45	F	N	Y	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	I	III ($T_3N_1M_0$)	+
32	3426/10	40	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
33	3460/10	60	M	N	Y	Y	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	III ($T_3N_1M_0$)	+
34	3484/10	53	M	N	N	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	I ($T_2N_0M_0$)	-
35	3536/10	45	F	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
36	3679/10	46	M	Y	N	N	RECTUM	POLYP	ADENOCARCINOMA	II		
37	3807/10	50	F	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
38	3812/10	42	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
39	3819/10	43	M	Y	N	N	RECTUM	POLYP	TUBULOVILLOUS			

									ADENOMA			
S.NO	**BIOPSY NO**	**AGE**	**SEX**	**BPR**	**ALT BH**	**LOW**	**SITE**	**CONFIGURATION**	**HPE**	**GRADE**	**STAGE**	**p53**
40	3830/10	52	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
41	3844/10	55	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
42	4023/10	50	M	N	N	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	III		
43	4044/10	40	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	I ($T_1N_0M_0$)	-
44	4127/10	43	M	Y	N	N	RECTUM	POLYP	TUBULAR ADENOMA			
45	4192/10	70	F	N	Y	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA		III ($T_3N_1M_0$)	+
46	4261/10	35	F	Y	N	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA			
47	4364/10	75	F	N	N	Y	RECTUM	ULCERO-PROLIFERATIVE	TUBULOVILLOUS ADENOMA			
48	4365/10	53	M	N	Y	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA			
49	113/11	51	F	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	S/O MALIGNANT MELANOMA			
50	218/11	57	M	N	Y	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	III ($T_4N_2M_0$)	+
51	364/11	40	F	Y	N	N	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	II ($T_3N_0M_0$)	-
52	417/11	62	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
53	722/11	42	M	Y	N	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
54	785/11	60	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
55	823/11	67	M	Y	N	N	ASCENDING COLON	POLYP	ADENOCARCINOMA	II		
56	862/11	67	M	Y	N	Y	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	III ($T_3N_1M_0$)	+
57	1236/11	28	F	N	Y	N	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	II ($T_4N_0M_0$)	-
58	1250/11	41	M	Y	N	N	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	IV ($T_3N_1M_1$) (M-Liver)	+
59	1439/11	50	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
60	1645/11	55	F	Y	N	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	I ($T_2N_0M_0$)	+
61	1689/11	70	F	Y	N	N	CAECUM	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA		II ($T_3N_0M_0$)	-
62	1840/11	40	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	III		
63	1992/11	45	F	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
64	2037/11	40	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	III	IV ($T_3N_1M_1$) (M-Ovary)	+
65	2124/11	65	M	Y	N	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	II	I ($T_2N_0M_0$)	-
66	2836/11	60	F	N	Y	N	CAECUM	POLYP	ADENOCARCINOMA	I		
67	2937/11	65	F	Y	N	N	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	I ($T_2N_0M_0$)	-
68	3101/11	49	F	N	N	Y	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	III ($T_2N_2M_0$)	-
69	3232/11	70	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
70	3384/11	40	M	Y	N	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	IV ($T_4N_1M_1$) (M-Liver)	-
71	3461/11	42	F	N	Y	N	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	II ($T_3N_0M_0$)	+

S.NO	BIOPSY NO	AGE	SEX	BPR	ALT BH	LOW	SITE	CONFIGURATION	HPE	GRADE	STAGE	p53
72	3701/11	66	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	VILLOUS ADENOMA			
73	3798/11	30	M	N	N	Y	ASCENDING COLON	ULCERO-PROLIFERATIVE	SIGNET RING CELL CARCINOMA			
74	3813/11	55	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	III		
75	4073/11	50	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA		II ($T_3N_0M_0$)	-
76	4227/11	39	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA		III ($T_3N_1M_0$)	-
77	4229/11	45	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA			
78	4272/11	55	M	N	N	Y	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
79	4289/11	45	F	Y	N	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	II	II ($T_3N_0M_0$)	+
80	4509/11	55	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	I ($T_2N_0M_0$)	
81	4324/11	70	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
82	4392/11	70	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
83	4529/11	67	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
84	4737/11	50	F	N	Y	N	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
85	4798/11	65	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	VILLOUS ADENOMA			
86	67/12	68	F	N	N	Y	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
87	194/12	52	F	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
88	315/12	65	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II		
89	419/12	45	F	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
90	519/12	65	F	N	N	Y	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	II	III ($T_3N_1M_0$)	+
91	559/12	50	F	Y	N	N	RECTUM	POLYP	ADENOCARCINOMA	II		
92	610/12	60	M	N	Y	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	I ($T_2N_0M_0$)	-
93	722/12	40	M	Y	N	N	ASCENDING COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	II ($T_3N_0M_0$)	-
94	723/12	38	M	Y	N	N	TRANSVERSE COLON	POLYP	ADENOCARCINOMA	II		
95	1027/12	20	M	N	Y	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	MUCINOUS CARCINOMA		III ($T_3N_2M_0$)	+
96	1189/12	55	M	N	Y	N	CAECUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	I ($T_2N_0M_0$)	+
97	1384/12	45	F	N	Y	N	TRANSVERSE COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I		
98	1522/12	70	M	Y	N	N	RECTUM	NARROWING OF LUMEN	ADENOCARCINOMA	II	III ($T_3N_1M_0$)	+
99	1992/12	62	M	Y	N	N	RECTUM	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	I	III ($T_4N_1M_0$)	-
100	2120/12	45	M	Y	N	N	SIGMOID COLON	ULCERO-PROLIFERATIVE	ADENOCARCINOMA	II	III ($T_3N_1M_0$)	+

HPE – Histopathological examination **LOW – Loss of weight**

BPR – Bleeding per rectum **ALT BH – Altered bowel habits**

S.NO	BIOPSY NO	AGE	SEX	SYMPTOMS	SITE	HPE	GRADE	P53
1	1093/10	52	M	INTESTINAL OBSTRUCTION	ILEUM	NHL/MALTOMA		
2	211/11	56	M	INTESTINAL OBSTRUCTION	JEJUNUM	MALIGNANT MELANOMA DEPOSIT		
3	273/11	27	M	INTESTINAL OBSTRUCTION	DUODENUM	NHL		
4	302/11	40	F	INTESTINAL OBSTRUCTION	DUODENUM	BENIGN GIST		
5	381/11	3	F	ABDOMINAL MASS	DUODENUM	BURKITT LYMPHOMA		-
6	888/11	50	M	INTESTINAL OBSTRUCTION	DUODENUM	ADENOCARCINOMA	II	+
7	1677/11	35	F	BLEEDING PER RECTUM	DUODENUM	ADENOCARCINOMA	II	-
8	1933/11	50	M	INTESTINAL OBSTRUCTION	DUODENUM	ADENOCARCINOMA	II	
9	2092/11	32	F	ABDOMINAL PAIN	DUODENUM	ADENOCARCINOMA	I	+
10	4726/11	50	M	INTESTINAL OBSTRUCTION	ILEUM	MALT-LYMPHOMA		+
11	1538/12	70	M	INTESTINAL OBSTRUCTION	JEJUNUM	MULTIPLE LIPOMA		

Figure 01: Multiple lipomatous polyp – Jejunum

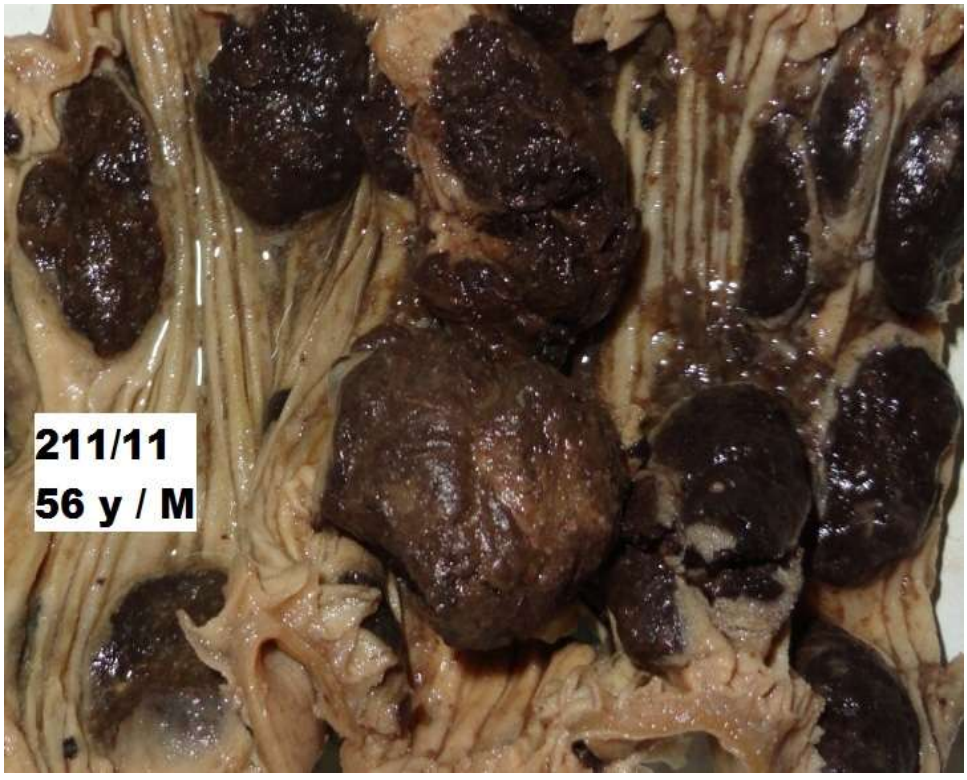


Figure 02: Malignant melanoma deposits – Jejunum showing multiple localized polypoid lesions

Figure 03: Ulceroproliferative growth sigmoid colon – Adenocarcinoma

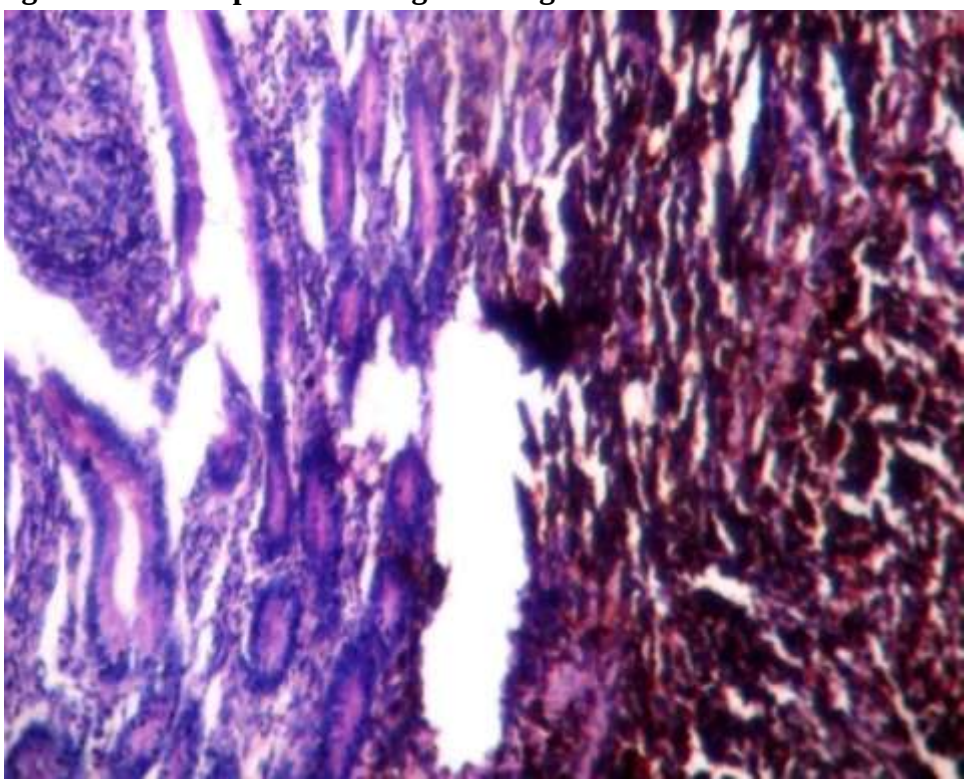


Figure 04: Malignant melanoma deposits – Jejunum showing sheets of atypical melanocytes with nuclear pleomorphism and prominent nucleoli with intracytoplasmic melanin pigment infiltrating into the submucosa [10X]

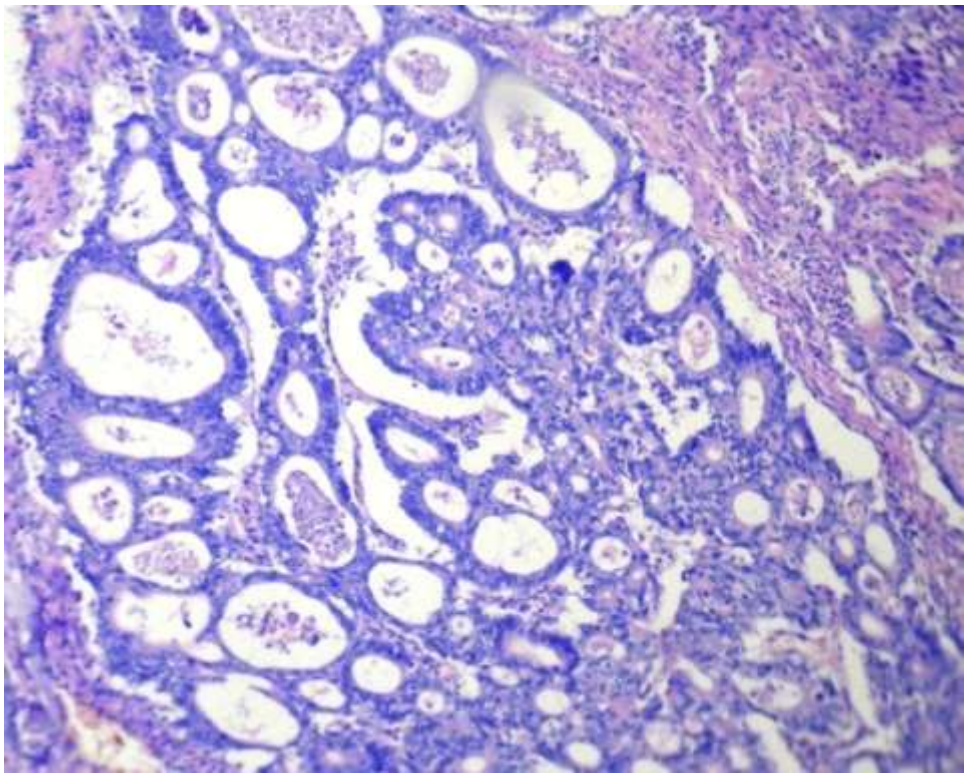


Figure 05: Well differentiated adenocarcinoma – Duodenum showing tubular glands lined by malignant cells [10X]

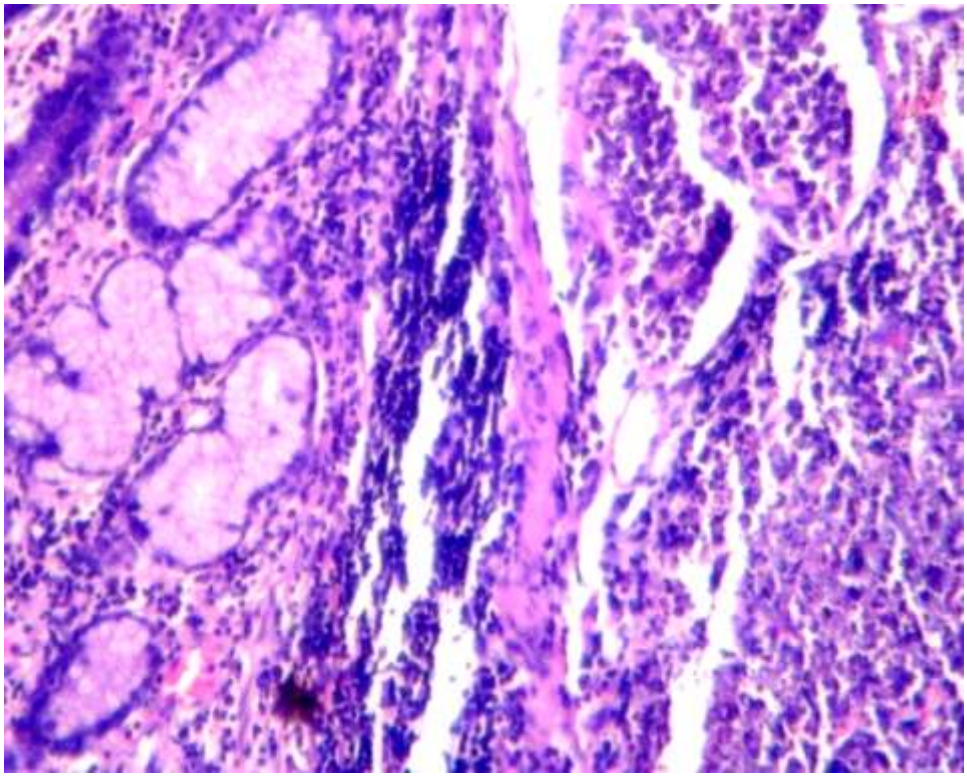


Figure 06: MALT Lymphoma – Ileum shows diffuse sheets of large atypical cells with irregular nuclear contour. Normal glands are seen above the lesion [10X]

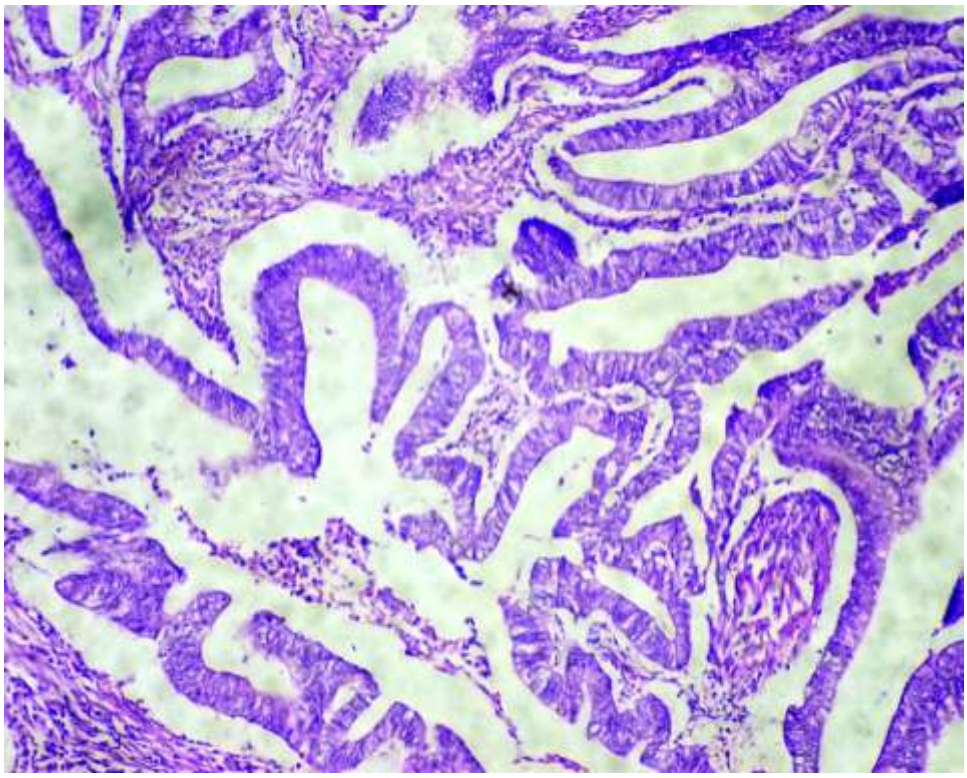


Figure 07: Well differentiated adenocarcinoma – Colon showing easily discernible tubule formation and basally oriented nuclei [10X]

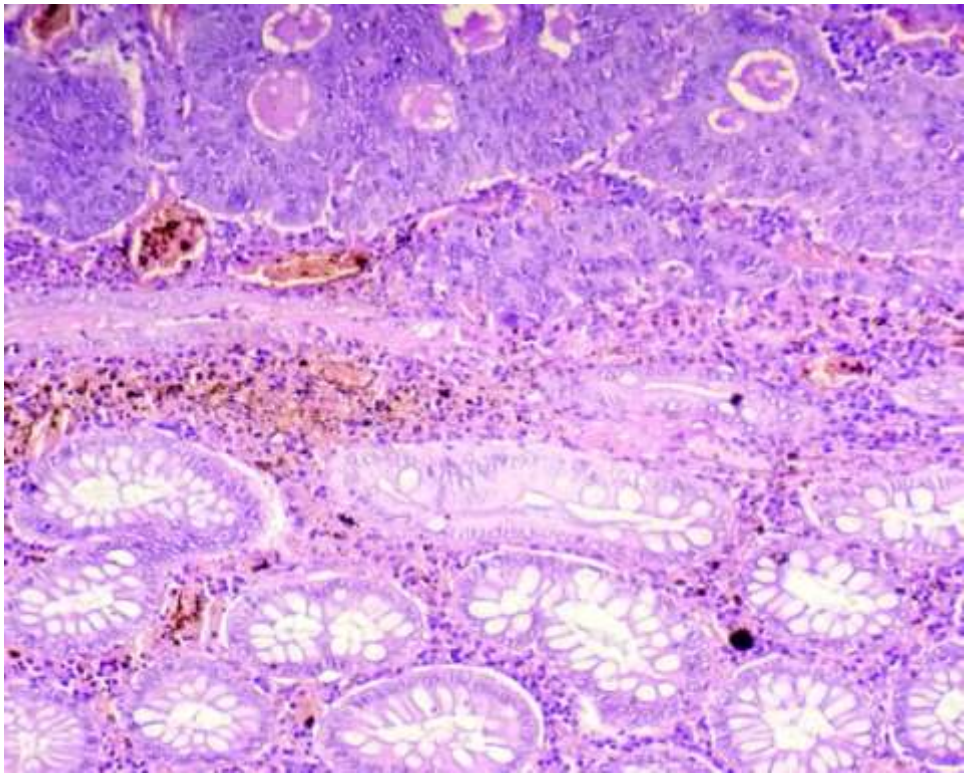


Figure 08: Moderately differentiated adenocarcinoma – Colon exhibiting a complex and irregular tubular pattern with some loss of nuclear polarity [10X]

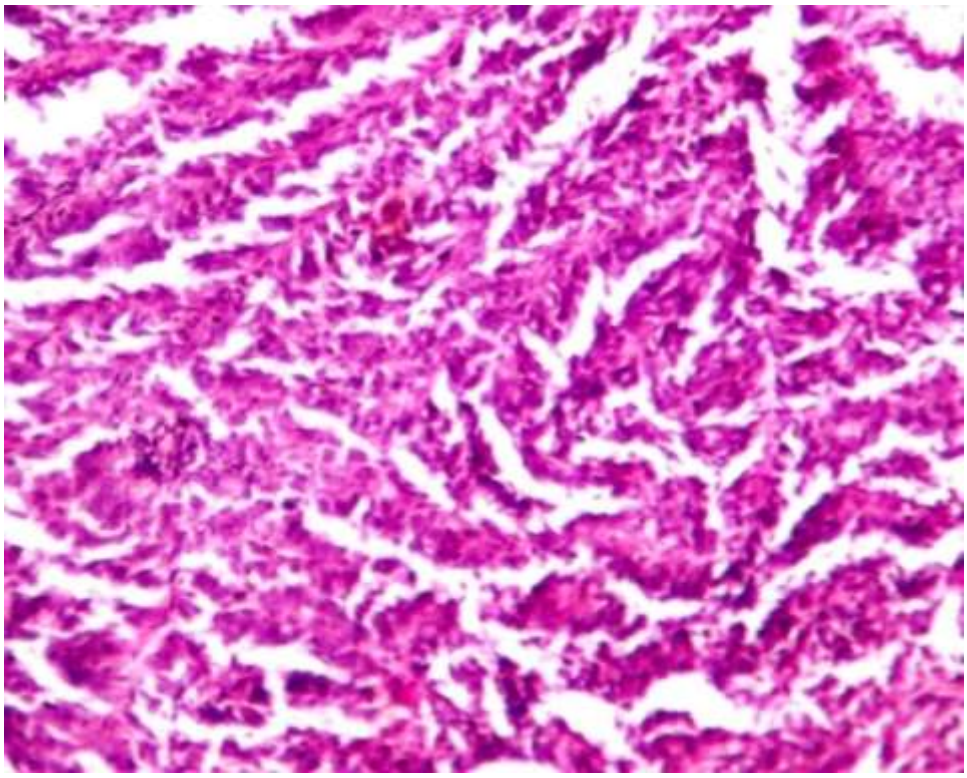


Figure 09: Poorly differentiated adenocarcinoma – Rectum showing diffuse sheets of malignant cells [10X]

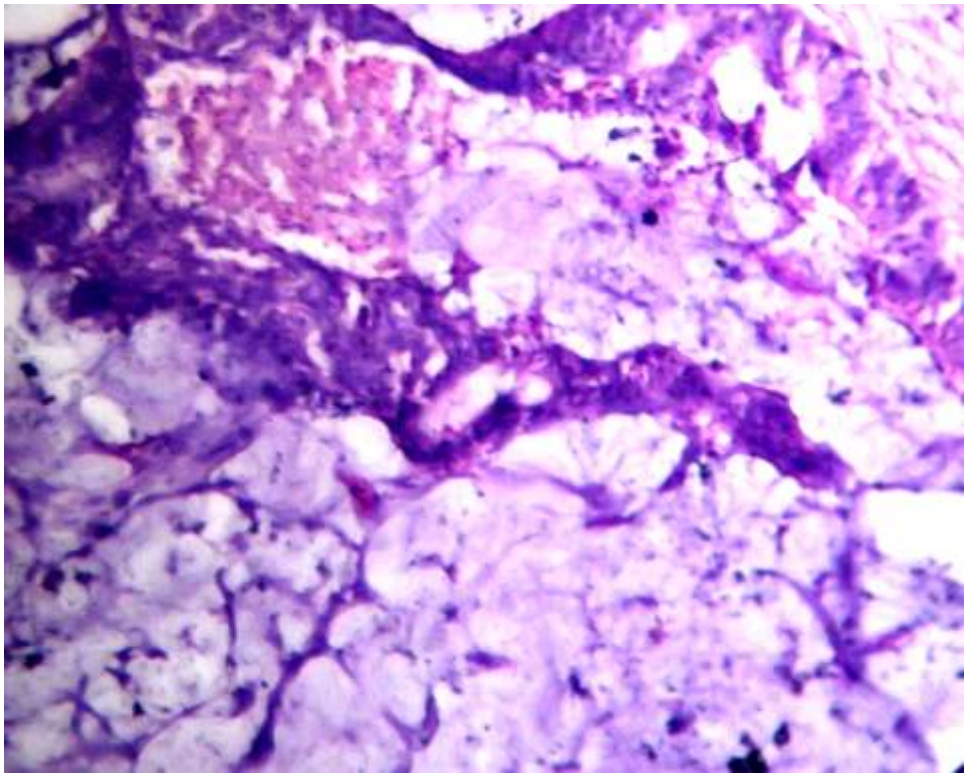


Figure 10: Mucinous adenocarcinoma – Colon showing malignant cells floating in mucinous pool [10X]

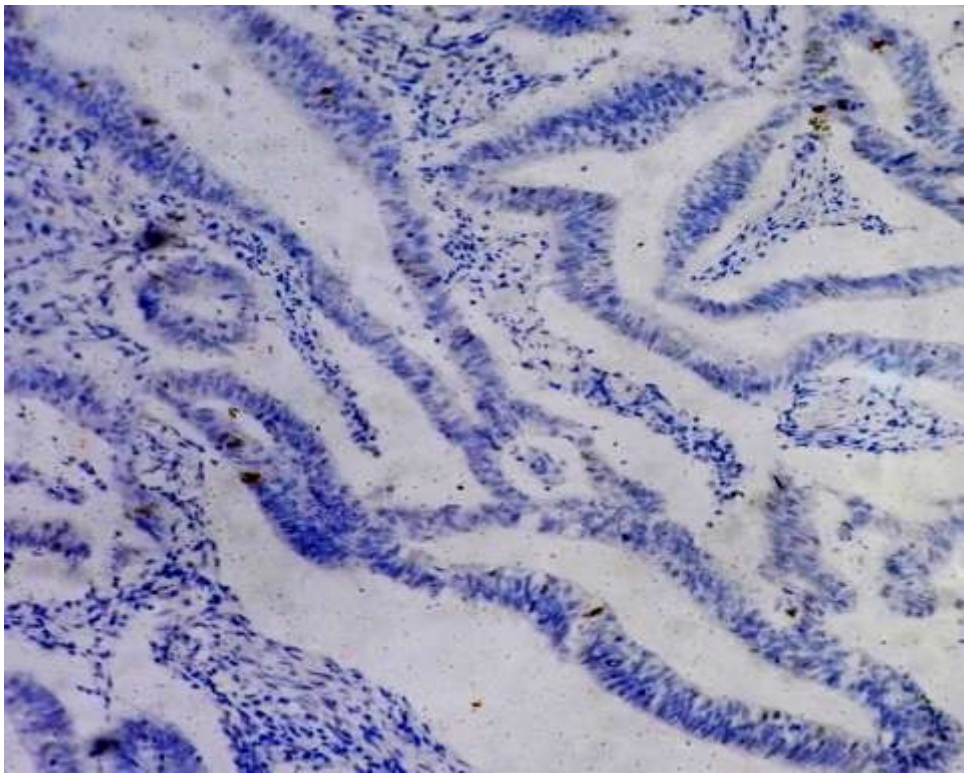


Figure 11: Stage I Colorectal carcinoma p53 Negative [10X]

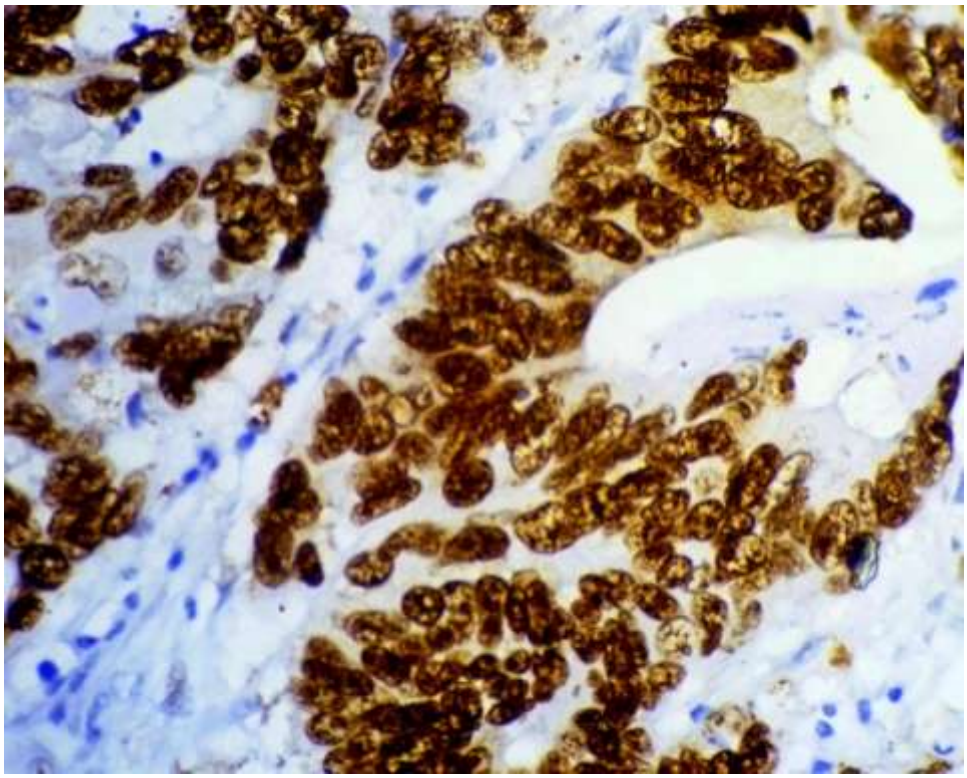


Figure 12: 23 StageI Colorectal carcinoma p53 Positive [40X]

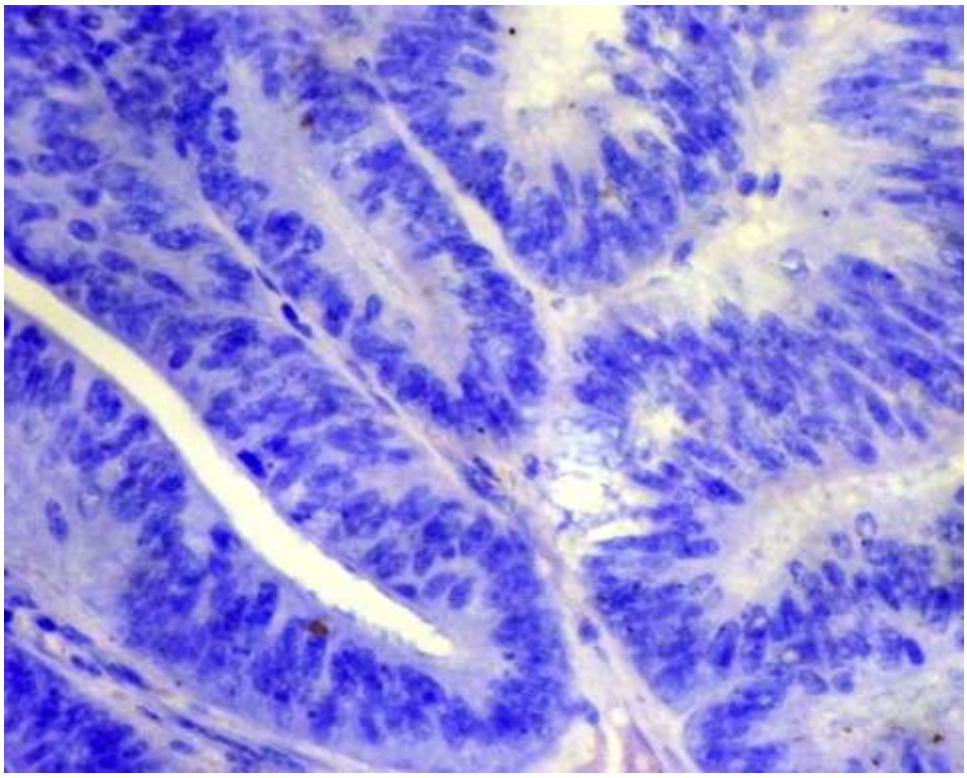


Figure 13: Stage II Colorectal carcinoma p53 Negative [10X]

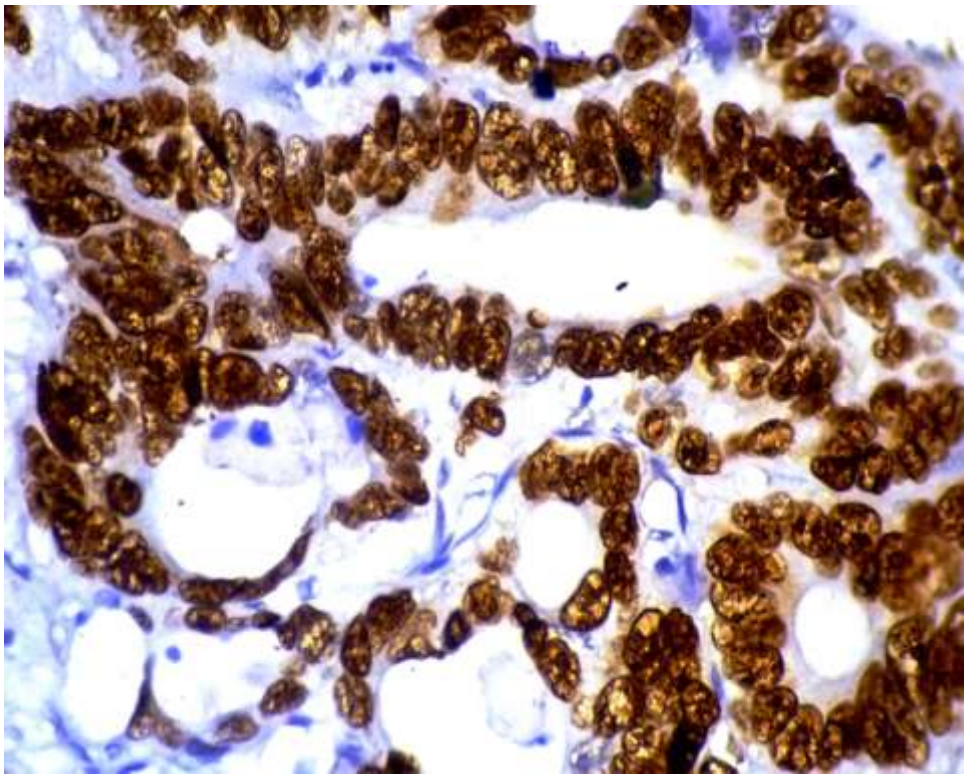


Figure 14: stageII Colorectal carcinoma p53 Positive [40X]

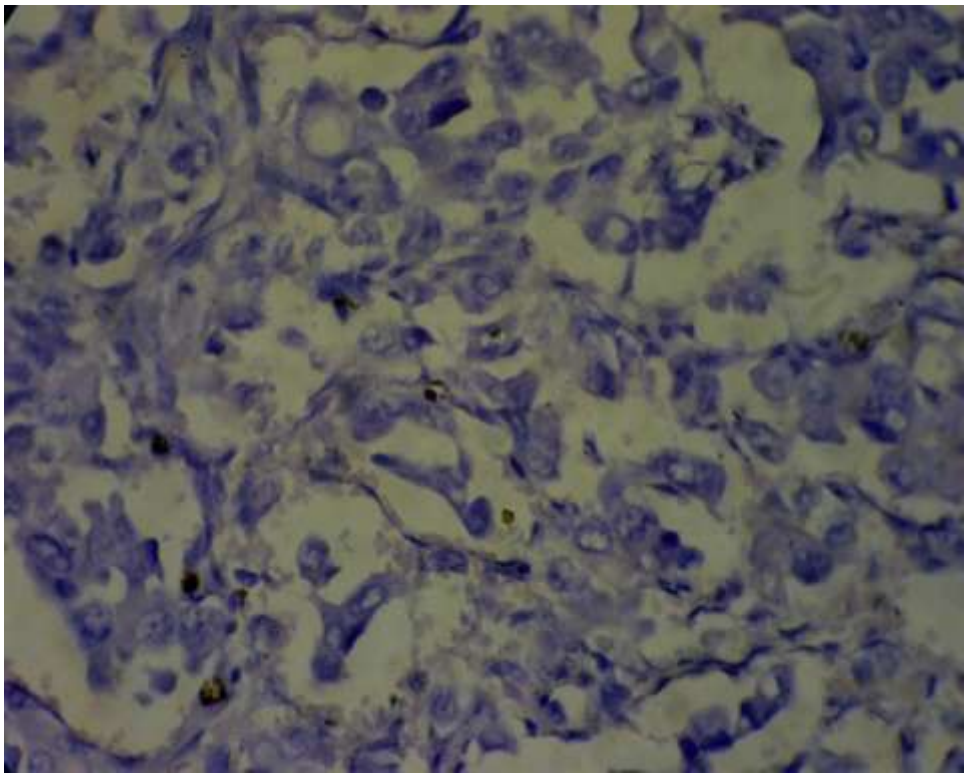


Figure 15: Stage III Colorectal carcinoma p53 Negative [10X]

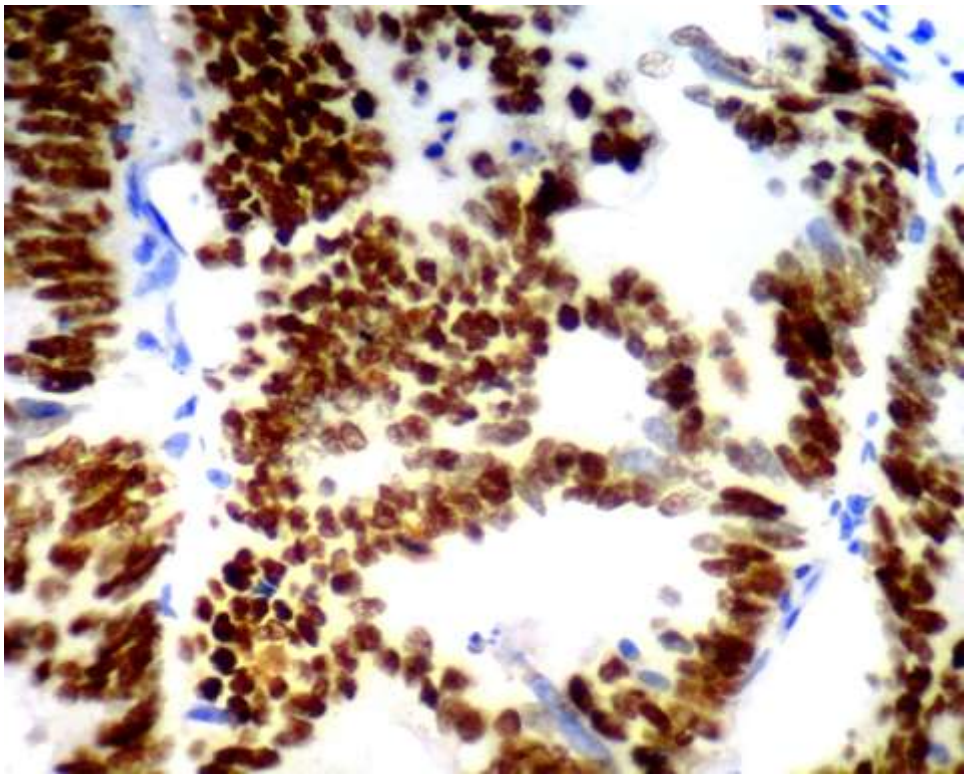


Figure 16: StageIII Colorectal carcinoma p53 Positive [40X]

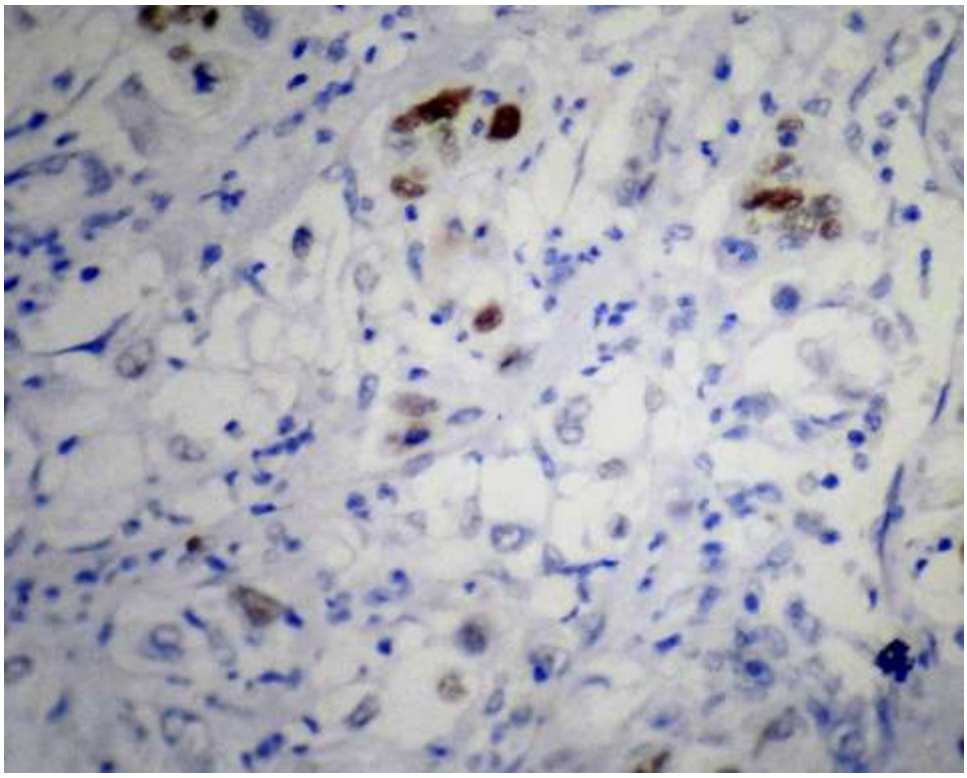


Figure 17: Stage IV Colorectal carcinoma p53 Negative [10X]

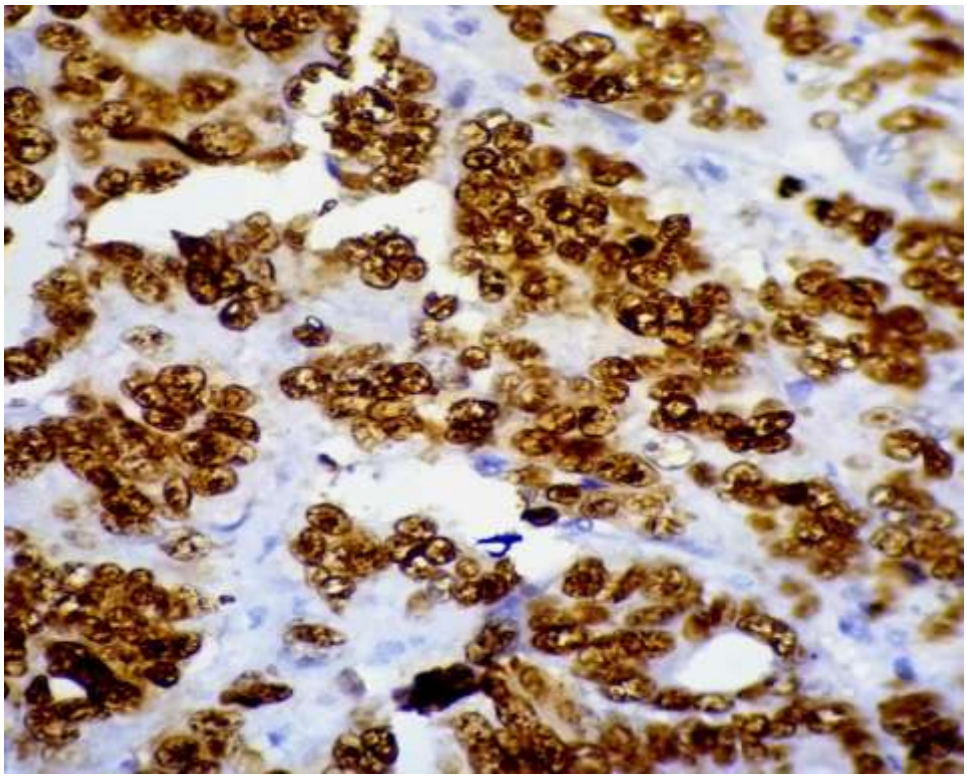


Figure 18: Stage IV Colorectal carcinoma p53 Positive [40X]

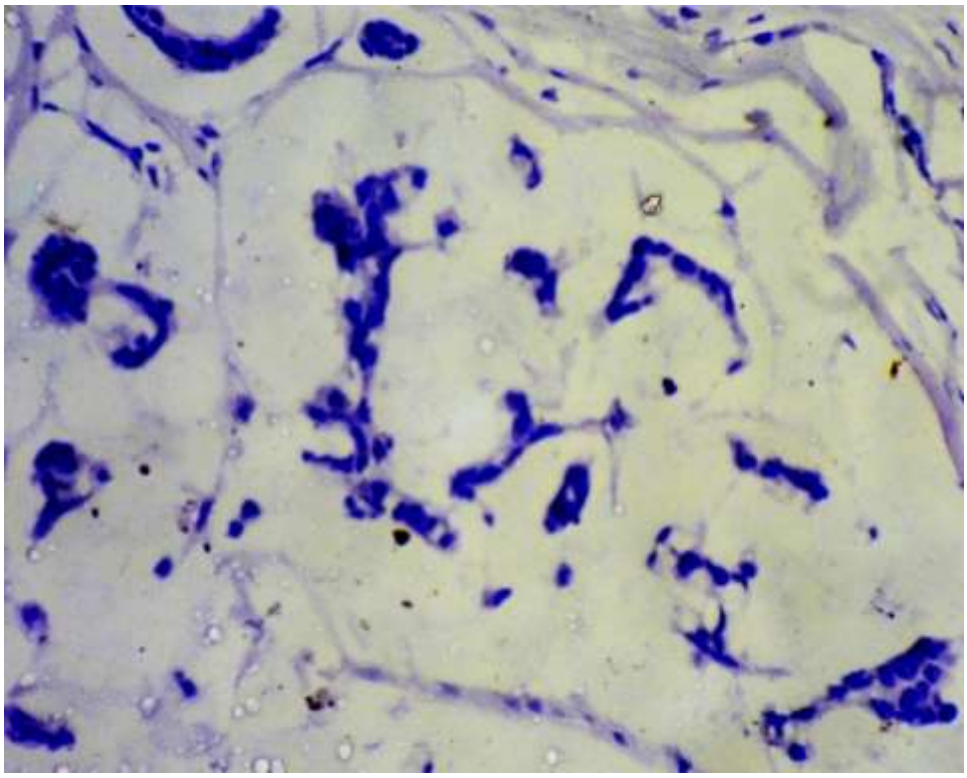


Figure 19: Mucinous adenocarcinoma p53 negative [40X]

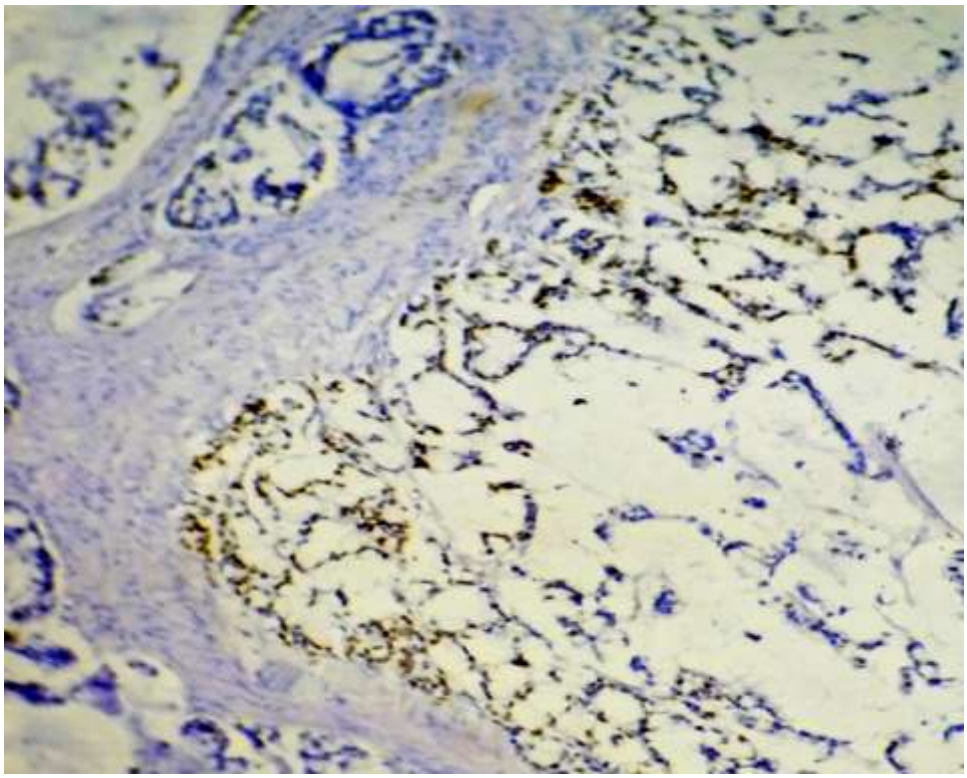


Figure 20: Mucinous adenocarcinoma p53 Positive [40X]

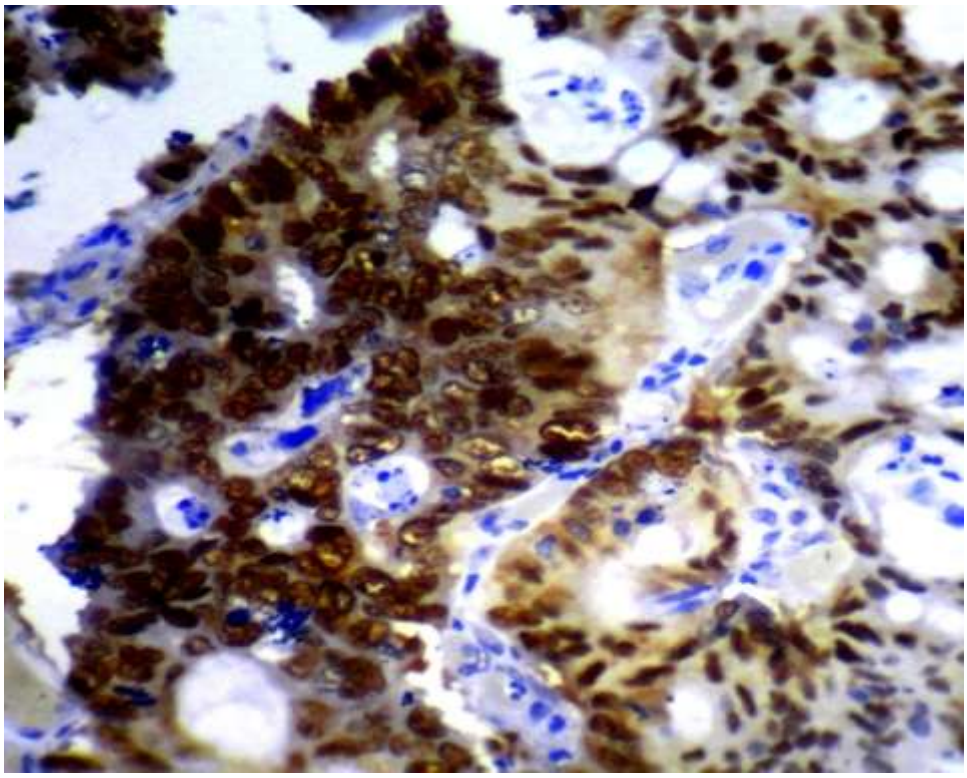


Figure 21: Small intestine adenocarcinoma p53 Positive [40X]

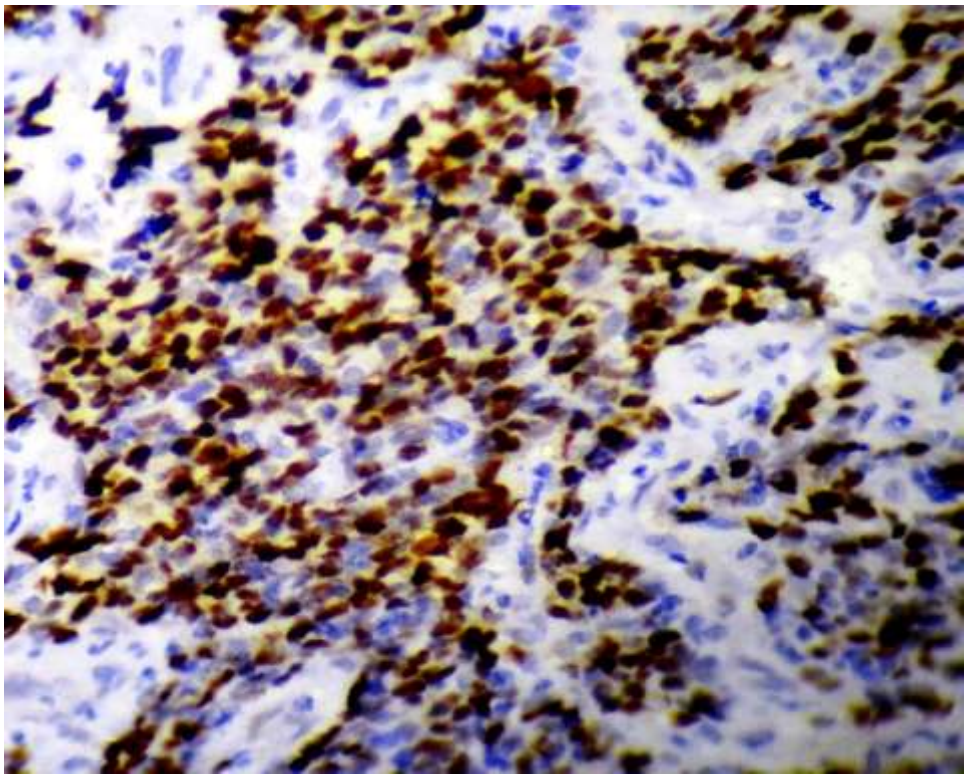
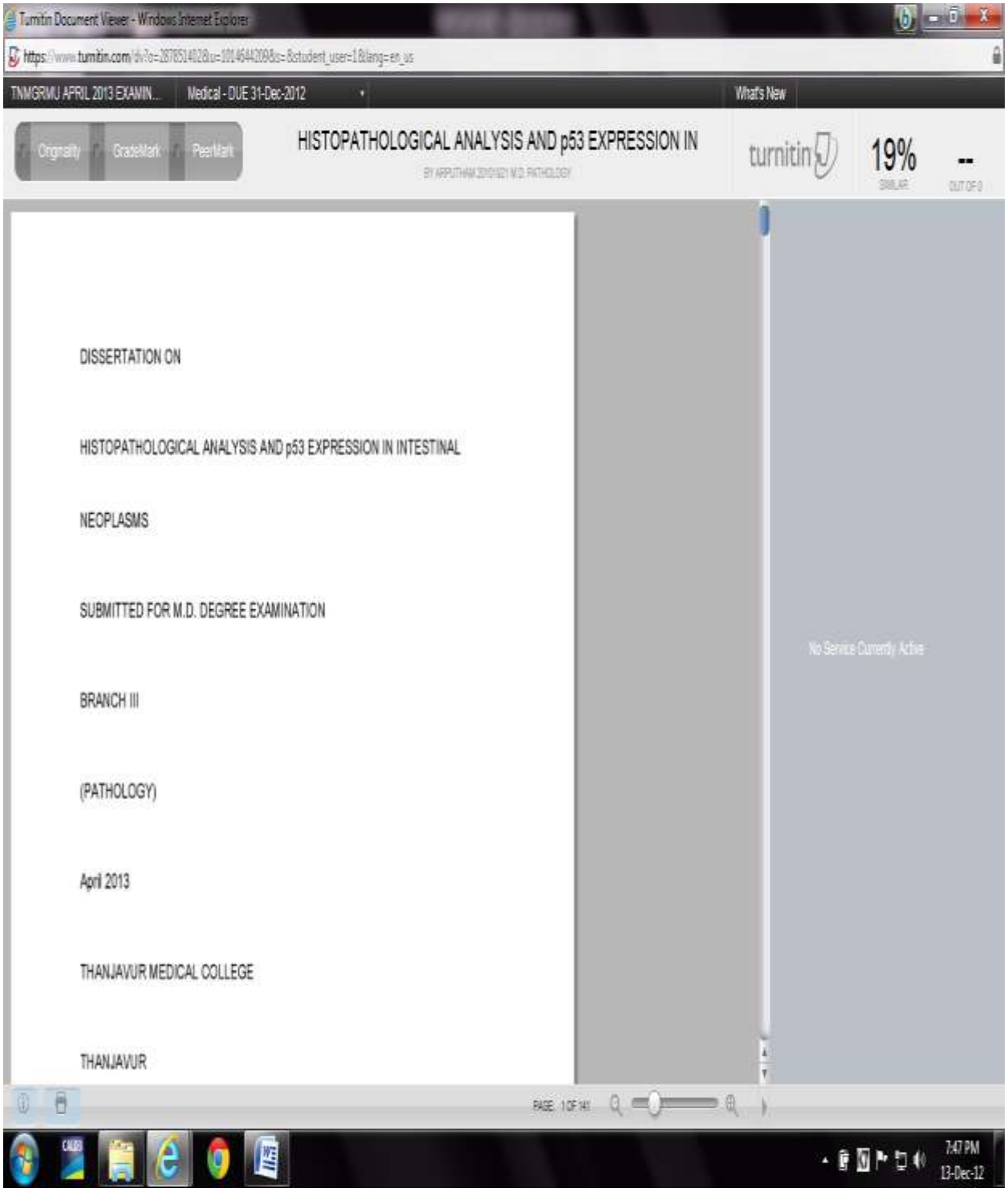


Figure 22: Small intestine Lymphoma p53 Positive [40X]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