IDENTIFICATION OF PREDICTIVE FACTORS FOR RESECTABILITY IN NON-METASTATIC CARCINOMA RECTUM.

A dissertation submitted in the partial fulfilment of MS General Surgery (Branch I) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in the year 2020

REG NO : 221511452

BONAFIDE CERTIFICATE

This is to certify that this is a bonafide work of **DR.EVANGELINE PREETI JENNIFER** submitted in partial fulfillment of the rules and regulations to Dr. M.G.R Medical University, Chennai for the M. S. branch – I (General Surgery) examination to be held in the year 2020.

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DECLARATION

This is to declare that the dissertation entitled "I**DENTIFICATION OF PREDICTIVE FACTORS FOR RESECTABILITY IN NON-METASTATIC CARCINOMA RECTUM"** " in the Department of General Surgery is my own work under the guidance of Dr.Mark Ranjan Jesudasan, Professor and Head of General Surgery Unit II and Dr.Suchita Chase , Professor General Surgery Unit IV, and submitted to the Dr.M.G.R Medical University in partial fulfillment of the rules and regulations for the M.S branch – I (General Surgery) examination to be held in the year 2020.

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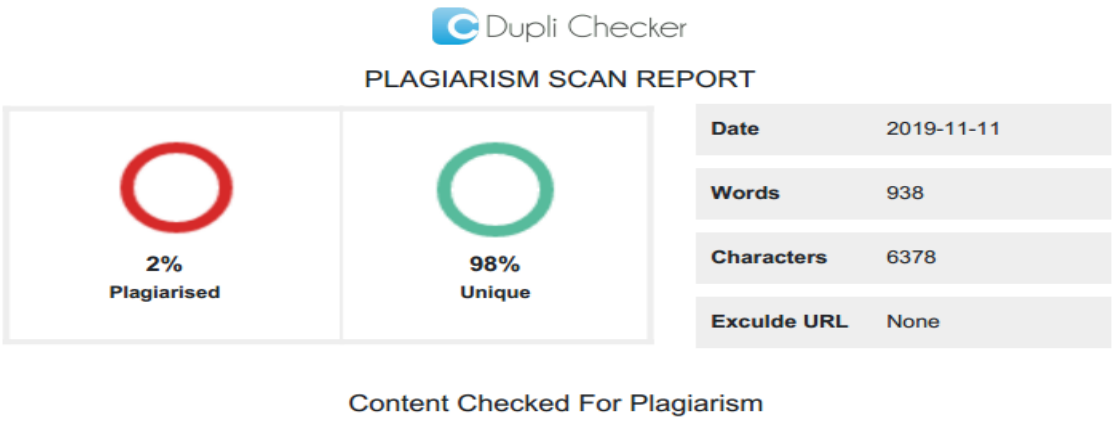

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Nowhere is the drive to do better more important than in medicine, where lives are on the line with every decision.

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“Sometimes we can offer a cure, sometimes only a salve, sometimes not even that. But whatever we can offer, our interventions, and the risks and sacrifices they entail, are justified only if they serve the larger aims of a person’s life. When we forget that, the suffering we inflict can be barbaric. When we remember it the good we do can be breathtaking.”
— Atul Gawande, Being Mortal: Medicine and What Matters in the End

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ABBREVIATIONS

1	SRA	superior rectal artery
2	IMA	inferior mesenteric artery
3	GI	gastrointestinal
4	PET/CT	positron emission tomography/computed tomography
5	CEA	carcinoembryonic antigen
6	MRI	Magnetic resonance imaging
7	ASCO	American Society of Clinical Oncology
8	TNM	tumor node metastasis
9	CRM	circumferential radial margins
10	TME	Total mesorectal excision
11	TaTME	Transanal TME
12	EMVI	Extramural vascular invasion
13	TRG	Tumour Regression grade

“We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do.”
— Atul Gawande, Complications: A Surgeon's Notes on an Imperfect Science

INTRODUCTION

Colorectal cancer is the third most common cancer in the world. Approximately 60% of cases are seen in developed countries. In the United States there are approximately 43,030 newly diagnosed rectal cancer patients each year (2).It is also the third most common cause of female mortality and second most common cause of male mortality in the United States (3).

In India, in men, colon cancer is the 8th and rectal is the 9th most common cancer seen in men. However, in women, rectal cancer is less common than colon cancer which is the 9th most common cancer (1).

Treatment of rectal cancer is multimodal and includes surgical resection of the tumour, chemotherapy and radiotherapy. The modality used depends on the stage of the disease at the time of diagnosis as well as many other factors. However, surgery remains the mainstay of treatment.All patients with a newly diagnosed rectal cancer require complete evaluation and staging, which includes :

- History and physical examination.
- Routine laboratory tests, including CEA
- Radiological imaging including MRI of the pelvis.
- Histopathology report
- Colonoscopy

After complete evaluation and staging all patients should be discussed in tumor board meeting and treatment plan made.

JUSTIFICATION

The treatment of non metastatic rectal carcinoma has changed over the years. While surgery continues to be the mainstay of treatment, current practice is to offer multimodal therapy to improve outcomes for patients. Other modes of treatment available include:

- Neoadjuvant Radiotherapy: Preoperative radiation (along with chemotherapy) is used for locally advanced rectal malignancies to downstage tumours. This often results in lower local recurrence rates. Also, some tumours which were earlier deemed inoperable, may become smaller in size and be amenable to surgery. Radiotherapy for downsizing is usually provided as a long course chemoradiotherapy, along with radiosensitising chemotherapy.
- Chemotherapy: Chemotherapy as part of the treatment regime has proven to be very effective in advanced stage rectal cancer. This includes preoperative (neo adjuvant) and post operative (adjuvant) chemotherapy.

Large tumors, deemed to be inoperable, may be offered neoadjuvant long course chemoradiation followed by a long wait, to reassess operability. Some of these tumors may become operable, however many will remain inoperable.

This study was designed to assess risk factors in the preoperative period, which would predict those patients who do not respond to neoadjuvant therapy and remained inoperable.

AIMS AND OBJECTIVES

AIM

- To identify predictive factors for resectability in non-metastatic carcinoma rectum

OBJECTIVES

- To identify clinical , pathological and radiological factors to predict risk for resectability in non metastatic carcinoma rectum.

REVIEW OF LITERATURE

SURGICAL ANATOMY

Rectum

Rectum is the continuation of the sigmoid colon extending below to the anal canal. It is 12 to 15 cm in length. It is characterized by the absence of taeniae, epiploic appendices, haustra and a well-defined mesentery. In women, the anterior rectum is in close proximity to the posterior vagina and uterine cervix . In men, it is behind the bladder, vas deferens, seminal vesicles and prostate.

The proximal limit of the rectum is at the rectosigmoid junction and the distal limit is at the dentate line. The dentate line is the transition point from columnar mucosa of the rectum to squamous mucosa of the anus. Radiologically, the upper limit of rectum is at the sacral promontory, while on endoscopy, it is 15 cm from the anal verge.

The rectum has three lateral curves corresponding to the valves (folds) of Houston. The upper and lower curves are convex to the right, and the middle is convex to the left. Once the rectum is

mobilized, these valves are no longer present and are responsible for the increase in length gained during the surgical dissection. The rectum is located below the peritoneal reflexion. The posterior rectal wall, which is close to the sacral hollow, is entirely extraperitoneal. The upper rectum is invested by peritoneum anteriorly and laterally, and the middle rectum is invested by peritoneum only anteriorly.

The fascia propria is an extension of the pelvic fascia and encloses the rectum, adipose tissue, blood, and lymphatic vessels. It is more pronounced laterally and posteriorly and forms the lateral ligaments of the rectum. Mesorectum is areolar tissue around the rectum that is thicker posteriorly and contains the terminal branches of the inferior mesenteric artery.

The rectum occupies the sacral concavity and ends 2 to 3 cm proximal to the tip of the coccyx. The presacral fascia covers the concavity of the sacrum and coccyx, presacral nerves, the middle sacral artery, and presacral veins. Distal rectal cancers are located 4 to 8 cm from the anal verge, mid rectal cancers are located 8 to 12 cm from the anal verge, and proximal rectal cancers 12 to 15 cm. The anal canal is 0 to 4 cm from the anal verge. However, surgical decision making for sphincter preservation is depends on the distance from the lower border of the tumor to the top of the anorectal ring rather than the anal verge.

Arterial blood supply

The upper rectum is supplied by the superior rectal artery (SRA), a branch of the inferior mesenteric artery (IMA). The middle and lower rectum are supplied by the middle rectal artery

and inferior rectal artery, respectively, which is a branch of the anterior division of the internal iliac artery .

Venous and lymphatic drainage

The lymphatic drainage of the upper two-thirds of the rectum is along the pathway of the superior hemorrhoidal vein, to the inferior mesenteric nodes and the paraaortic nodes. The lymphatic drainage of the lower third of the rectum is along the middle hemorrhoidal vessels to the internal iliac nodes. Below the dentate line, the drainage is along the inferior rectal lymphatics to the superior inguinal nodes and along the pathway of the inferior rectal artery.

Innervation

All pelvic nerves lie in the plane between the peritoneum and the endopelvic fascia, hence are at a risk of being injured during rectal dissection. The preganglionic fibers via the sympathetic nerves follow the branches of the Inferior Mesenteric Artery and the Superior Rectal Artery to the left colon and upper rectum. The presacral nerves , which consists of the aortic plexus and lumbar splanchnic plexus innervate the lower rectum. Just below the sacral promontory, the presacral nerves form the hypogastric plexus. The main hypogastric nerves enter the rectum laterally and carry sympathetic innervation from the hypogastric to the pelvic plexus, located on

the lateral side of the pelvis , at the level of the lower rectum. The parasympathetic plexus emerges through the sacral foramen and joins the sympathetic hypogastric nerves at the pelvic plexus. Postganglion parasympathetic and sympathetic fibers are distributed to the left colon and upper rectum via the inferior mesenteric plexus and directly to the lower rectum and upper anal canal.

RECTAL CARCINOMA

There has been a rapid increase in incidence of colorectal carcinoma. There has been an estimate of 18.1 million new cancer cases and 9.6 million deaths caused by colorectal cancer in year 2018(1) . It is also considered as the second highest cause of deaths. The estimated 5-year cancer prevalent cases are shown below. In 2018, there were 4,789,635 patients who had been diagnosed as having colorectal cancer within the previous 5 years. Though some studies show a slight male predominance, based on 2018 data o newly diagnosed colorectal carcinoma, there was an equal distribution between men (2,595,326)and women (2,194,309) .The 5-year prevalence of CRC was 62.8/100,000 and it is ranked the second among all cancer types based on 2018 WHO statistics(2).

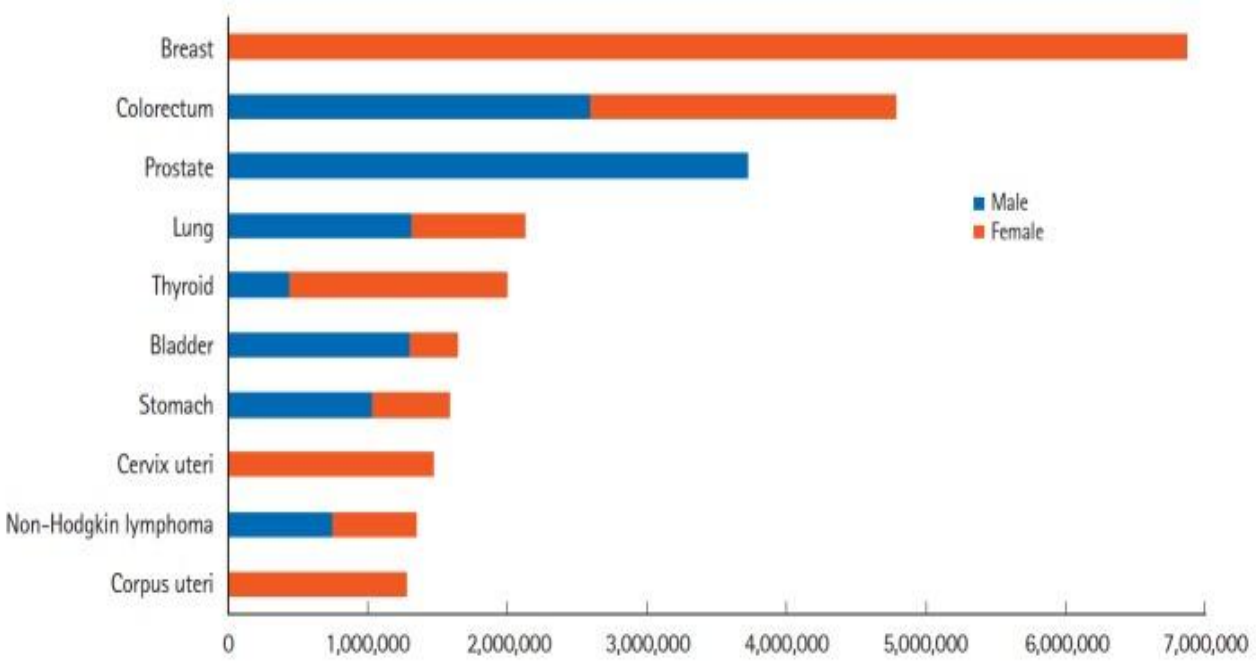


Figure 1: Estimated 5-year cancer prevalent cases in 2018 (top 10). There were 4,789,635 patients (2,595,326 men and 2,194,309 women) who had been diagnosed as having colorectal cancer within the previous 5 years. Data source: International Agency for Research on Cancer, GLOBOCAN 2018, World Health Organization (WHO)

There are various factors that affect the presence of colorectal carcinoma. They include age, gender, ethiniciy, body mass index, diet etc(3). Of these age is an important factor(4). It is seen that the risk of developing colorectal carcinomaincreases dramatically after age 50 years . 90% of all CRCs are diagnosed after 50 years old. The incidence rate of colorectal cancer in the United States increased sharply after age 40 years and rates for male subjects were significantly higher than that in female subjects. Some western studies show that obesity is associated with colorectal cancer, however an Asian study shows that there is correlation between obesity and colon cancer but not with rectal cancer(5).

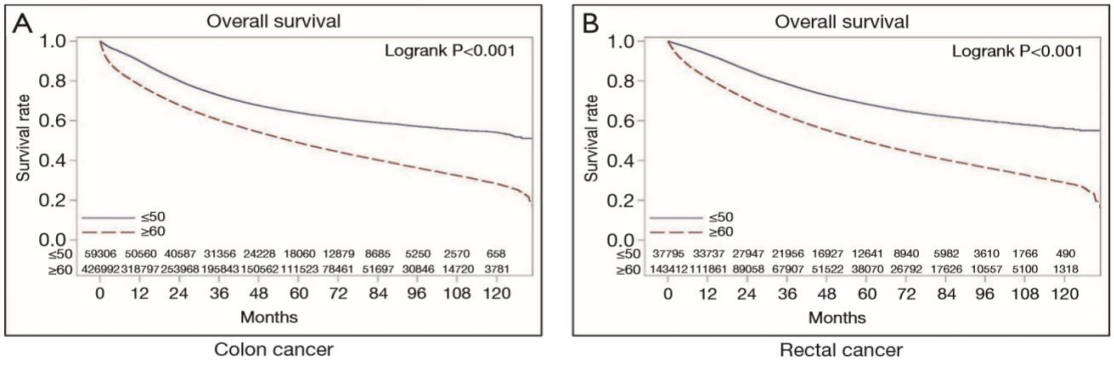


Figure 2 : Overall survival of patients with colon cancer (A) and rectal cancer (B) by age ≤50 and ≥60, adjusted by Charlson-Deyo comorbidity status.

Patient characteristic	Group, n (%)		Overall, n (%)
	≤50 years	≥60 years	
Overall	37,979 (20.9)	143,930 (79.1)	181,909 (100.0)
Gender*			
Male	21,750 (57.3)	82,771 (57.5)	104,521 (57.5)
Female	16,229 (42.7)	61,159 (42.5)	77,388 (42.5)
Race			
White	31,322 (82.5)	125,270 (87.0)	156,592 (86.1)
Black	4,131 (10.9)	11,606 (8.1)	15,737 (8.7)
Other	2,526 (6.7)	7,054 (4.9)	9,580 (5.3)
Ethnicity			
Not Hispanic	32,270 (91.3)	126,390 (94.9)	158,660 (94.2)
Hispanic	3,062 (8.7)	6,725 (5.1)	9,787 (5.8)

Table-1 Baseline characteristics of patients with rectal cancer from the NCDB, years 2004–2013, based on available data

Clinical presentation of rectal cancer(6)

Patients with colorectal cancer may present in three ways:

- Suspicious symptoms and signs as mentioned below
- Asymptomatic individuals diagnosed with cancer during routine screening

- Emergency admission with intestinal obstruction, peritonitis, or rarely, an acute gastrointestinal (GI) bleed

Local symptoms —

In a retrospective cohort study of a total of 29,000 patients conducted at a colorectal surgery clinic over a period of 22 years , the most common symptoms that were noted in patients with colorectal carcinomaincluded :

- change in bowel habits (74%)
- Rectal bleeding in combination with change in bowel habits (51 % of all cancers and 71% of those presenting with rectal bleeding)
- Rectal mass (24.5 %)
- Iron deficiency anemia (9.6%)
- Abdominal pain was the least common symptom (3.8%).

In another study conducted from 2011 to 2014 among 388 patients diagnosed with colorectal carcinoma, anemia was more common than altered bowel habits. These patients underwent diagnostic colonoscopy and the primary presentation for the group was as follows:

- Bleeding per rectum (37 percent)
- Abdominal pain (34 percent)
- Anemia (23 percent)
- 6 patients (1.9 percent) had incidental colonic hypermetabolic activity detected by a positron emission tomography/computed tomography (PET/CT) image that was being done for another reason.

● 4 patients (1.3 percent) underwent diagnostic colonoscopy because of change in bowel habits (diarrhea).

Clinical manifestations may also depend on tumor location:

● Abdominal pain may be present due to partial obstruction, peritonealdisease, or perforation with generalized peritonitis.

●Rectal cancer can cause tenesmus, rectal pain, and diminished caliber of stools.

Metastatic disease

Patients can also present with signs and symptoms of metastatic disease(7). Approximately 20 percent of patients in the United States have distant metastatic disease at the time of presentation . Metastasis can be by lymphatic and hematogenous dissemination, as well as by contiguous and transperitoneal routes. The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum. Patients may present with signs or symptoms depending on the site of the metastatic lesion. These symptoms include right hypochondrial pain, jaundice, cough with hemoptysis and rarely abdominal distension .On examination they may have hepatomegaly,

abdominal mass, ascites, supraclavicular lymphadenopathy, periumbilical nodules in advanced and metastatic disease. Since the venous drainage is through the portal system, the first site of hematogenous dissemination is usually the liver, followed by the lungs, bone, and other sites, rarely including the brain. Tumors arising in the distal rectum may metastasize initially to the lungs because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.

DIAGNOSIS

For all patients with a newly diagnosed rectal cancer, a pretreatment staging evaluation is required(8)(9).The purpose of this study was to evaluate the diagnostic efficiency of colorectal carcinoma (CRC) with the tumor markers Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA 19-9), in addition to investigating whether CA 19-9 can be used to screen the disease process in patients with CRC who had no elevation of CEA levels. Methods: Serum levels of CEA and CA 19-9 were measured in: 138 patients with CRC; 111 patients with benign colorectal diseases. The diagnostic value was performed using the logistic regression equation and receiver operating characteristic curves (ROC). Results: The serum levels of CEA and CA 19-9 in the patients with CRC were significantly higher than those in the patients with benign colorectal diseases ($P < 0.001$).

Receiver operating characteristic curves (ROC) in the patients with CRC versus those with benign colorectal disease yielded the optimal cut-off value of 3.36 ng/ml for CEA and 23.9 U/ml for CA 19-9, respectively. The area under ROC curve (AUC) was 0.789 for CEA, 0.690 for CA 19-9 and 0.900 for the combination of the two tumor markers. The combination resulted in a higher Youden index and a sensitivity of 85.3%. Conclusion: The combined detection of serum CEA and CA 19-9 could play a pivotal role in the diagnosis of CRC, and could drastically improve the sensitivity for the diagnosis of CRC. CA 19-9 might be a tumor biomarker in addition to CEA for

(10).

It consists of :

- History and physical examination.
- Laboratory tests, including liver function tests and a carcinoembryonic antigen (CEA) level.
- Rigid proctosigmoidoscopy and digital rectal examination (assessment of thedistance of tumour from the anal verge, mobility and position in relation to the anal sphincter).
- Magnetic resonance imaging (MRI) or endorectal ultrasound to assess the local extent of the tumor.
- Colonoscopy to assess for synchronous colonic lesions.
- Computed tomography (CT) of the chest, abdomen, and pelvis to assess for metastatic disease.

Laboratory tests

For diagnosis of rectal carcinoma there is no role for routine blood investigations. In case of complication due to the disease, e.g. Hemoglobin can be checked in case o iron deficiency anemia due to bleeding per rectum. Similarly liver function tests can be done incase of metastasis to liver, however it is not a sensitive test for metastasis.

Tumor markers

A variety of serum markers have been associated with CRC, including carcinoembryonic antigen (CEA)(10). However, they have a low diagnostic ability to detect primary CRC due to significant overlap with benign disease and low sensitivity for early-stage disease .

Group	N	CEA (ng/ml)	CA 19-9 (U/ml)
CRC	138	5.60 (2.08-11.25)	21.60 (11.45-46.00)
Benign colorectal disorder	111	1.73 (1.17-2.45)	13.00 (7.60-19.00)

Mann-Whitney U test was carried out between the two groups: CEA (Z = -7.843, P < 0.001), CA 19-9 (Z = -5.159, P < 0.001).

Table-2 shows the concentrations of CEA and CA 19-9 were statistically different among the two groups (Z = -8.826--8.609, all P < 0.001). The levels of CEA and CA 19-9 were significantly higher in CRC group than those in benign colorectal disorder group

Based on a meta-analysis, the pooled sensitivity of CEA for diagnosis of CRC was only 46 percent (95% CI 0.45-0.47) . No other conventional tumor marker had a higher diagnostic sensitivity, including carbohydrate antigen 19-9 (pooled sensitivity 0.30, 95% CI 0.28-0.32).

Also, specificity of CEA is limited. Other causes for elevatedCEA include gastritis, peptic ulcer disease, diverticulitis, liver disease, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammatory state. It is also seen that, CEA levels are significantly higher in cigarette smokers than in non-smokers.

Table 1: Patient characteristics

	r-CEA < 5 (n=479)	r-CEA ≥ 5 (n=266)	*p*
Median disease free interval (range, months)	16.4 (0.9-158.0)	15.8 (0.7-118.4)	
Gender			0.390
Male	314 (65.6%)	166 (62.4%)	
Female	165 (34.4%)	100 (37.6%)	
Median age (range, years)			
Initial pT-stage			0.089
pT0-2	116 (24.2%)	50 (18.8%)	
pT3-4	363 (75.8%)	216 (81.2%)	
Initial pN-stage			< 0.001
pN0-1	344 (71.8%)	155 (58.3%)	
pN2-3	135 (28.2%)	111 (41.7%)	
Initial CEA			< 0.001
CEA < 5	383 (80.0%)	118 (44.4%)	
CEA ≥ 5	96 (20.0%)	148 (55.6%)	
Initial treatment			0.899
Surgery alone	228 (47.6%)	132 (49.6%)	
Surgery + adjuvant CCRT	101 (21.1%)	57 (21.4%)	
NACRT + Surgery	144 (30.1%)	75 (28.2%)	
Preop RT + Surgery	6 (1.2%)	2 (0.8%)	
Pattern of failure			0.064
LRR	91 (19.0%)	51 (19.2%)	
DM	323 (67.4%)	162 (60.9%)	
LRR + DM	65 (13.6%)	53 (19.9%)	
Treatment after recurrence			< 0.001
Salvage treatment	165 (34.4%)	54 (20.3%)	
Surgery +/- CCRT	140 (29.2%)	37 (13.9%)	
RT +/- chemo	9 (1.9%)	10 (3.8%)	
RFA only (for liver metastasis)	16 (3.3%)	7 (2.6%)	
Palliative or conservative	248 (51.8%)	183 (68.8%)	
Unknown	66 (13.8%)	29 (10.9%)	

CEA, carcinoembryonic antigen level; CCRT, concurrent chemoradiotherapy; NACRT, neoadjuvant chemoradiotherapy; LRR, locoregional recurrence; DM, distant metastasis; RT, radiation therapy; RFA, radiofrequency ablation

. *Table The characteristics of patients according to CEA group*(11)

An expert panel on tumor markers in breast and colorectal cancer convened by the American Society of Clinical Oncology (ASCO) recommended that neither serum CEA nor any other marker, including CA 19-9, should be used as a screening or diagnostic test for CRC.

A similar recommendation has been made by the European Group on Tumor Markers . However, CEA level is valuable in the follow-up of patients with diagnosed CRC. ASCO guidelines recommend that serum CEA levels be collected in CRC patients preoperatively to help in posttreatment follow-up, and in the assessment of prognosis(12).

Before surgery	**At recurrence**					
	<5 ng/mL	**≥5 ng/mL**	***p***	**<10 ng/mL**	**≥10 ng/mL**	***p***
Relation between serum CEA levels before surgery and those at recurrence in 106 patients with recurrence						
<5 ng/mL (*n* = 34)	19 (55.9%)	15 (44.1%)	<0.001	25 (73.5%)	9 (26.5%)	<0.001
≤5 ng/mL (*n* = 72)	18 (25.0%)	54 (75.0%)		31 (43.1%)	41 (56.9%)	

Before surgery	**After surgery**					
	<5 ng/mL	**≥5 ng/mL**	***p***	**<10 ng/mL**	**≥10 ng/mL**	***p***
Relation between serum CEA levels before surgery and those after surgery in 677 patients without recurrence						
<5 ng/mL (*n* = 352)	343 (97.4%)	9 (2.6%)	<0.001	352 (100%)	0 (0%)	<0.001
≥5 ng/mL (*n* = 325)	201 (61.8%)	124 (38.2%)		303 (93.2%)	22 (6.8%)	

Relation between serum CEA levels before surgery and at recurrence/after surgery(12)

Serum levels of CEA have prognostic utility in patients with newly diagnosed CRC. Patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with

lower levels, however other data concludes that elevated preoperative CEA that normalizes after resection is not an indicator of poor prognosis .

Elevated preoperative CEA levels that do not normalize following surgical resection suggests the presence of disease, requiring more evaluation and management.

A rising CEA level after surgical resection implies recurrent disease and should prompt follow-up radiologic imaging. Hence it is suggested by various studies that a serial assay of postoperative CEA levels should be performed for five years for patients with stage II and III disease if they may be a potential candidate for surgery or chemotherapy if they are diagnosed with metastatic disease.

Colonoscopy

Colonoscopy is the most accurate and versatile diagnostic test for CRC, since it can localize the tumor and also biopsy lesions, detect synchronous neoplasms, and remove polyps. Synchronous CRCs, defined as two or more distinct primary tumors diagnosed within six months of an initial CRC, separated by normal bowel, and not due to direct extension or metastasis, occur in 3 to 5 percent of patients (13).

The tumors appear as endoluminal masses that arise from the mucosa and protrude into the lumen . The masses may be exophytic or polypoid. Bleeding (oozing or frank bleeding) may be seen with lesions that are friable, necrotic, or ulcerated. Circumferential or near-circumferential involvement of the bowel wall correlates with the so-called "apple-core" description seen on

radiologic imaging. A few of the neoplastic lesions in the gastrointestinal tract are nonpolypoid and relatively flat or depressed.

The methods for tissue sampling of larger visible lesions include biopsies, brushings, and polypectomy. For lesions that are completely removed endoscopically (with polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection), tattooing is important for subsequent localization if an invasive neoplasm is found, and additional local therapy is needed. Tattoos are usually placed adjacent to or a few centimeters distal to the lesion.If a malignant obstruction precludes a full colonoscopy preoperatively, the entire residual colon should be examined soon after resection.

STAGING OF RECTAL CANCER

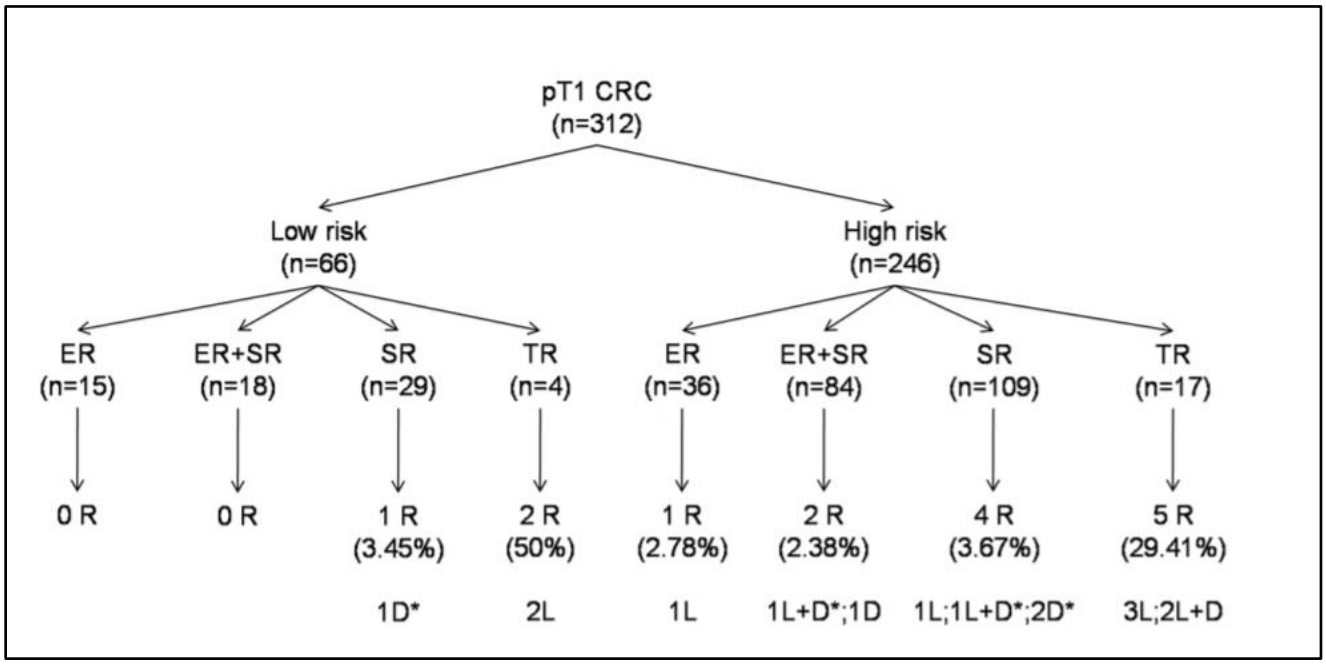
Based on the pre treatment evaluation of the patients newy diagnosed with rectal cancer , the patients are staged based on the tumor node metastasis (TNM) staging system recommended by the American Joint Committee on Cancer(14) . Staging helps in tailoring treatment to each individual, including a combination of surgery/ chemotherapy and radiotherapy. Staging also helps in prognosticating the disease.

The TNM staging is as follows:

Table -1 TNM Staging

T1	Tumor involves the submucosal layer

T2	Tumor involves the muscularis propria but no extension is seen into the perirectal tissues
T3	Tumor extends into the perirectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor involves adjacent organs
N1	1–3 regional lymph nodes
N1a	1 positive regional lymph node
N1b	2–3 positive regional lymph nodes
N1c	Tumor deposit(s) in the perirectal tissues without nodal metastases
N2	≥4 positive regional lymph nodes
N2a	4–6 positive regional lymph nodes
N2b	≥7 positive regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis present in only 1 organ or site
M1b	Distant metastasis present in >1 organ/site or peritoneal metastases



Flow diagram summarizing the patients with local and distant recurrences and cancer-related deaths by histopathological risk factors and treatment strategies. CRC: colorectal cancer; ER: endoscopic resection only; ER+SR: endoscopic resection followed by surgical resection; SR: surgical resection only; TR: trans anal resection; R: recurrence; D: distant recurrence; L: local recurrence; L+D: local and distant recurrence; *patients with cancer-related deaths(15).

MANAGEMENT OF RECTAL CANCER

Rectal cancers , like several other malignancies , are treated with a multidisciplinary approach(16). In most patients surgery continues to play an important role in treatment with curative intent. For example, some patients with limited invasive cancer in a polyp may have no other adverse features. For such patients polypectomy alone may be enough. For others who have locally extensive, fixed, bulky tumors or extensive nodal disease, induction chemoradiotherapy or induction chemotherapy followed by chemoradiotherapy may be used as the best treatment option. Majority of cases require a combination of 2 or all 3 modalities of treatment. Decision for each patient is made by a multidisciplinary team depending on their preoperative evaluation . Chemotherapy and radiotherapy can be delivered either as adjuvant or as neoadjuvant therapy(17).

PRINCIPLES OF SURGICAL RESECTION

The primary aim of surgery for rectal cancer includes a wide resection of the rectal cancer to obtain histologically negative margins. The secondary aim remains is to reestablish intestinal continuity and preserve anorectal function (fecal continence)(18).

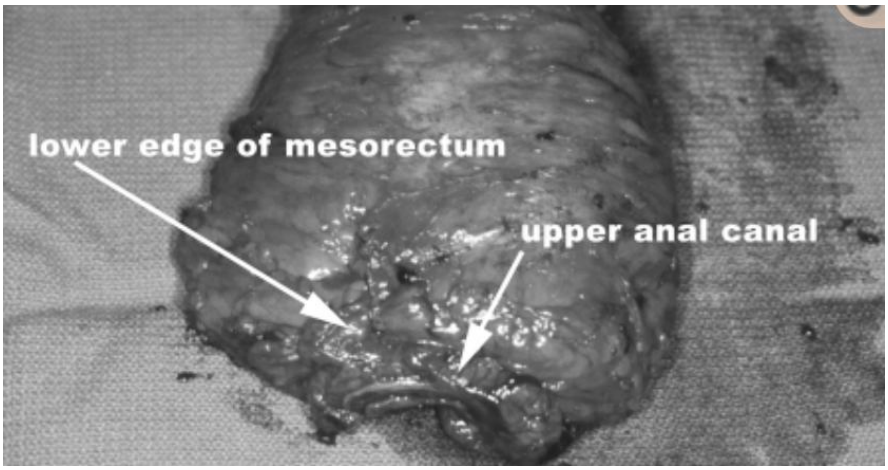


Figure : Mesorectal excision specimen

In this total mesorectal excision specimen, one can see that the mesorectum ends just above the upper aspect of the surgical anal canal, which is at the anorectal angle. During a double stapled coloanal anastomosis, the anus is divided at the anorectal angle, and the anastomosis will be constructed ~1.5 to 2.0 cm above the dentate line.

Resection margins

The primary goal of surgery for rectal cancer is to achieve histologically negative proximal, distal, and radial margins(19).

Proximal margin

Surgery is planned so as to obtain a minimum of 5 cm of proximal margin so as to ensure that the draining lymphatics are removed along with the tumour(20).

Distal margin

Minimum recommended negative distal margin is 2 cm for most sphincter-sparing procedures. However, for tumours located at or below the distal mesorectal margin, a 1-cm negative distal margin can be considered acceptable in the setting of neoadjuvant chemoradiation therapy. If the surgeon is unable to obtain the minimum negative margin, it is an indication to convert / plan for an APR, which extends the distal margin to the anus. For upper rectal cancers, a 5-cm distal margin distal to the tumor is acceptable. A positive distal margin was associated with a local recurrence rate approaching 40 percent (hazard ratio [HR] 16.8, 95% CI 4.8-5.9) and a decreased five-year survival (HR 2.35,95% CI 1.08-5.11) , even with the use

of TME and adjuvant radiotherapy.

Radial margins

In rectal surgery, the circumferential radial margins (CRM) are as important as the distal margin(21). A histologic CRM of greater than 1 mm is required. However, in one large cohort study, as many as 17 percent of patients undergoing rectal cancer surgery had a positive CRM . A positive CRM is an independent predictor of local recurrences and inferior survival . The risk of having a positive CRM is increased in patients with locally advanced tumors . Hence, patients identified on presurgical staging evaluation to have tumor within 2 mm of the mesorectal fascia should receive neoadjuvant therapy to reduce the risk of having a positive CRM. During APR, the levator ani muscle should be resected en bloc with the rectum and anal canal to avoid CRM involvement or perforation. The various surgical procedures include local excision , sphincter sparing procedures and abdominal perineal resection.

Local Excision:

It is recommended for mobile, stage T1, well or moderately differentiated tumours in the distal rectum with no vascular or lymphatic invasion that are less than 3 cm in diameter and involve less than 30% of the rectal wall circumference(22) . These tumours should also have no evidence of nodal disease on preoperative ultrasound or MRI. The other indication for local excision includes palliation of more advanced cancer in patients with severe comorbid disease, in whom extensive surgery carries a high risk for morbidity or mortality. The procedure involves a trans anal approach with excision of the full thickness of the rectal wall underlying the tumor. In these cases, the incidence of lymphatic metastases is less than 8 % . However, tumours in this region that invade or penetrate the muscular wall have a higher incidence of local recurrence (>20%), hence in these patients only local excision would be inadequate . Other disadvantage of local excision is that since it does not include mesorectal lymph nodal dissection operative staging would be incomplete(23).

Proctectomy with total mesorectal excision (abdominoperineal resection or low anterior resection) allows examination of the local lymph nodes and is associated with 5-year survival rates more than 95% for stage I T2N0 rectal cancers. In T2N0 lesion which are small (<3 cm) , distal, accessible and have no poor histopathologic features (poor differentiation, lymphovascular or perineural invasion), local excision in combination with chemoradiation may be indicated(24).

Total mesorectal excision (TME)

TME involves en bloc removal of the perirectal areolar tissue, including the lateral and circumferential margins of the mesorectum, lymphatics and tumor deposits with the primary rectal cancer(25). TME also preserves the autonomic nerves and reduces the risk of presacral bleeding.TME has replaced blunt dissection as the standard technique of removing perirectal tissue when performing radical rectal cancer surgery (sphincter sparing or APR). As the

rectum is 12 to 15 cm long, a complete removal of the mesorectum down to the pelvic floor is only necessary for mid and lower rectal malignancy . For upper rectal malignancy, the mesorectum only needs to be excised to a level of 5 cm below the primary tumor so as to obtain a negative resection margin.

TME technique(26)

Standard transabdominal TME — Standard TME is performed transabdominally with open, laparoscopic, or robotic techniques.

A standard TME for rectal cancer includes

● Removal of mesorectum, including the lateral and circumferential margins of the mesorectal envelope, to 5 cm below the distal margin of the primary tumor (in upper rectal cancer), or to the pelvic floor (in mid and lower rectal cancer)

● Removal of the blood supply and lymphatics of the origin of the superior rectal artery by ligating the inferior mesenteric artery (IMA) below the origin of the left colic artery (low tie

technique). Compared with ligating the IMA at its origin from the aorta (high tie technique), the low tie technique minimizes injury to the superior hypogastric plexus, which in turn minimizes postoperative urinary and sexual dysfunction.

Transanal TME (TaTME)

In experienced centers, TME has also been attempted transanally, particularly for distal rectal tumors in obese male patients with a narrow pelvis. Because the distal margin is assessed precisely from the beginning of the procedure, Transanal TME (TaTME) has the potential to define the resection margins more clearly than standard transabdominal TME(27)(28).

Studies with a follow-up of up to 2 years showed that TaTME had a similarlocal recurrence rate and survival rate to standard TME . Long-term oncologic outcomes of TaTME, however, have not been reported. Iatrogenic urethral injury has also been noted in men who underwent TaTME. Transabdominal TME remains the standard treatment for most patients with rectal cancer.

TME outcomes

TME is associated with improved local control and better survival, as well as decreased postoperative genitourinary dysfunction due to pelvic autonomic nerve preservation. The local recurrence rates of an APR or sphincter-sparing procedure with TME ranged from 4 to 7 percent.[In comparison, the local recurrence rates of the same procedures without TME ranged from 14 to 45 percent, depending upon whether or not adjuvant therapy was used]. The improvement in local recurrence rates with TME is attributed to improved clearance of tumor deposits from the mesentery, as well as a decreased risk of disrupting the mesentery and spilling

tumor cells during dissection. TME also preserves the pelvic autonomic nerves, which reduces the risk of postoperative genitourinary dysfunction(29).

Regional lymph node dissection

Lymph node dissection is performed for the purposes of staging, local control, and to prevent metastasis of the disease. It is achieved by removing the blood supply and lymphatics up to the level of the origin of the superior rectal artery. "High" ligation of the inferior mesenteric artery at the origin of the aorta, or extended lymph node dissection laterally, is not necessary in the absence of clinically positive nodes. Atleast 12 lymph nodes sampling has been adopted as a quality metric for colorectal cancer surgery by the American College of Surgeons, the College of American Pathologists, the National Comprehensive Cancer Network (NCCN), and the American Association of Clinical Oncology (ASCO). However, the use of neoadjuvant chemoradiation has been shown to reduce the number of lymph nodes that can be retrieved from the surgical specimen(30).

Abdominal Perineal Resection and Low Anterior Resection:

The rectum and sigmoid colon are mobilized through an abdominal incision. The pelvic dissection, done through the abdominal incision, mobilizes the mesorectum in continuity with the tumor-bearing rectum. The pelvic dissection extends upto the level of the levator ani muscles. The perineal part of the operation includes excision of the anus, anal sphincters, and distal rectum which is excised when adequate margins are not possible due to close proximity to anal sphincters(31). Anterior resection is the resection of rectosigmoid above the peritoneal reflection

and low anterior resection indicates that the operation entails resection of the rectum below the peritoneal reflection through an abdominal approach. For cancers involving the lower half of the rectum, the entire mesorectum should be excised along with the rectum. Total mesorectal excision, produces the complete resection of the rectum and its adjacent mesorectum, enveloped within the visceral pelvic fascia with uninvolved circumferential margins.

Total mesorectal excision has resulted in a significant increase in 5-year survival rates (50% to 75%), a decrease in local recurrence rates (30% to 5%), and a decrease in the incidence of impotence and bladder dysfunction (85% to <15%).

Radiotherapy :

Radiotherapy is not used as a primary modality in treatment of rectal carcinoma however several studies have proven its use in improving local control following surgery. The usual dose given is 45 Gy in 25 fractions of 1.8 Gy each. An additional tumor boost may be administered, usually through opposed lateral fields, to an additional 5.4 to 9 Gy. Details regarding dose o radiation and combined treatment with concurrent chemotherapy is given below under management of stages of rectal cancer(32).

Chemotherapy:

Chemotherapy aims to sterilize the micro-metastatic disease and facilitating the local control rates achieved by surgery and radiotherapy. Anti-metabolites (fluoropyrimidines) form the mainstay of chemotherapy in rectal cancers. Presently, the chemotherapeutic agents effective in

rectal cancers include platinum based compounds and camptothecins along with biological agents such as monoclonal antibodies against Epidermal Growth Factor Receptors (Cetuximab) and Vascular Endothelial Growth Factor receptors (Bevacizumab). Concurrent chemotherapy (5 fluorouracil) is also commonly practiced with radiation in treatment of rectal cancer because of its potentiating effect with radiation. Other newer drugs including oral fluoropyrimidines (capecitabine), oxaliplatin, and irinotecan, have been shown to be effective in the treatment of metastatic colorectal cancer(33)(17)(34).

Concurrent Chemoradiation :

National Comprehensive Cancer Network (NCCN) guidelines recommends preoperative concurrent chemoradiotherapy as a standard treatment for stage II/III rectal cancer. The recommended radiation dose is 45~50Gy in 25~28 fractions using multiple radiation fields (generally 3~4 fields technique).

European Society for Medical Oncology (ESMO) recommends short course radiotherapy (1 week, 25 Gy/5f) or long course radiotherapy (45-50.4 Gy/1.8-2 Gy), combined with 5-fluorouracil (5-FU). ESMO guidelines recommended that the treatment for rectal cancer should be stratified based on the recurrence risk. The recurrence risk is assessed by the pretreatment MRI including the tumor invasion depth (T staging), number of metastatic lymph nodes (N

staging) , the distance to anus, invasion of mesorectal fascia and extramural vascular invasion. Based on this the patients are divided into ultra-low-risk group, low-risk group, medium-risk group and high-risk group(35).

For ultra-low-risk group and low risk group (T1~2, early T3N0, tumor invasion depth less than 5 mm assessed by MRI, unaffected mesorectal fascia and extramural vascular invasion , if the tumor is located above the levator ani , middle and low rectal cancer) , the recommended treatment includes direct surgery. If pathology indicates adverse prognostic factors including metastatic lymph nodes or positive circumferential resection margin, post operative chemotherapy should be added (36).

For Medium-risk group (T2-3, T4a , tumor invasion depth more than 5 mm assessed by MRI, un-affected mesorectal fascia, or/and metastatic lymph nodes), neoadjuvant chemoradiotherapy can significantly reduce the local recurrence rate(36). Long course chemoradiotherapy can bring higher pCR rate and is currently the first choice of most radiotherapy centers.

For High-risk group (T3~T4b with mesorectal fascia invasion, or/and metastatic iliac lymph nodes), Long course chemoradiotherapy followed with TME (Total Mesorectal Excision) surgery after 6 to 8 weeks is the first choice and accepted treatment modalities for high-risk group patients. For elderly patients or patients who cannot tolerate long-term course of chemotherapy, 5×5Gy short course of radiotherapy can be considered.

RECENT STUDIES ON CARCINOMA RECTUM

INTERNATIONAL STUDIES

In a study published by Emmanuel Gabriel et al(3) in Journal of Gastrointestinal Oncology in 2018 February , they tried to identify differences in both demographic and pathologic factors associated with the age-related rates of colorectal cancer (CRC) and overall survival (OS). Using the National Cancer Data Base for patients from 2004- 2013 they divided the patients based on their age (< 50 vs > 60 years). A multivariable analysis was performed to identify factors associated with OS. A total of 670,030 patients were included.181,909 with rectal or rectosigmoid cancer. patients ≤50 years had higher proportions of pathologic stage III and IV disease than patients ≥60 (III: 35.8% *vs.* 28.6%, IV: 16.5% *vs.* 11.6%, respectively for age ≤50 and≥60 years; P≤0.001) .

Another study published in the European Journal of Cancer 2009(2), the association between duration of symptoms and colorectal cancer was studied among 4155 patients with symptom duration as an explanatory variable and tumour stage as a dependent variable .It was noted that there was an inverse relationship between symptom duration and colon cancer TNM-stage. However there was no correlation between rectal carcinoma and duration of symptoms.

In another study published in International Journal of Surgery by Eisar Al Sukhni et al(19) studied thepredictors of circumferential resection margin involvement in surgically resected rectal cancer. It was a retrospective study in which 13.3% had a positive CRM. Of these, 54.2% received neoadjuvant therapy in the form of chemotherapy (4.5%), radiation (2.5%), or both (47.2%). Adjuvant radiation and chemoradiation were administered in 2.8% and 12.2% of CRM positive patients, respectively . A third of the CRM positive patients didnot receive radiation as it was not part of the planned treatment (81.1%) or it was contraindicated due to patient risk factors (6.9%) or it was refused by the patient (5.8%).

Svenja Thies (37)et al in another study assessing the tumour regression grade in gastrointestinal tumours post neoadjuvant therapy. Tumor regression grading (TRG) systems aim to categorize the amount of regressive changes that are present after cytotoxic treatment that the patient receives inthe form of neoadjuvant therapy. It is the induced fibrosis in relation to residual tumor or the estimated percentage of residual tumor in relation to the previous tumor site. There are various different TRG systems depending on the site of tumour. The two commonly used grading systems for rectal cancer the Dworak or the Rödel grading system(38) . The system more commonly used is the Rodel Grading System. Patients with pathological complete regression showed improved disease-free survival, decreased risk of local recurrence and improved overall survival.

In another retrospective study published in Journal of Clinical Pathology in 2012 conducted by MacGregor TP et al (39), said that patients with pathological complete regression showed improved disease-free survival, lower risk of local recurrence, better chance of being free from

distant metastasis and increased overall survival. TRG, especially in terms of complete regression, therefore is considered to representing a potential tool to guide therapy in patients with rectal cancer as well.

INDIAN STUDIES :

A study conducted by J.Nath et al in a Tertiary centre in India (CMC, Vellore) in 2009(40). The aim of this study was to determine the relative incidence of rectal cancer in young patients (< 40 years) in India and identify any differences in histological grade and pathological stage between younger and older cohorts. There were 102 patients involved in this study from September 2003 to August 2007. It was noted that 35.5% of the patients were less than 40 years of age and were more likely to present with less favourable histological features (52.0%*vs* 20.5% (P < 0.001)) and low rectal tumours (63.0%*vs* 50.0%) (P = 0.043) . However they were equally likely to undergo curative surgery compared to the older group (P = 0.629). Younger patients undergoing surgery had a higher pathological T stage (T0–2 18.9%, T3 62.3%, T4 19.7%*vs* 34.5%, 56.0%, 9.5%) (P = 0.027) and higher pathological N stage (N0 31.1%, N1 41.0%, N2 27.9%*vs* 53.4%,26.7%, 17.2%) (P = 0.014).

In another Indian study by Ruhina Shirin Laskaret al in Assam ,144 patients were studied in view of analysing the frequency and clinicopathological characteristics of rectal cancer patients. Of this70 (48.61%) were below 40 years and 74 (51.39%) were ≥40 yr of age. The mean age at presentation was 43. 4 ± 15.8 yr, the youngest patient was 14 years old. The younger patients had predominance of low rectal tumours, advanced T-stage, poor differentiation with mucinous and signet ring and an advanced disease stage as compared to the older patients.

METHODOLOGY

The study was conducted in the Department of Surgery Unit II, Christian Medical College and Hospital , Vellore. Patients who were diagnosed with non metastatic carcinoma rectum during the period January 2015 to December 2017 were recruited in the study.

STUDY DESIGN

This was a case control study. Cases were defined as patients who underwent rectal resection, and controls were patients who were inoperable, even after neoadjuvant therapy.

INCLUSION CRITERIA

- All patients diagnosed to have carcinoma rectum
- Planned for neoadjuvant therapy followed by surgery

During the study period (Jan 2015 -Dec 2017)

EXCLUSION CRITERIA

Patients with

1 . Metastatic carcinoma rectum

2 . Received neoadjuvant therapy at another centre

OUTCOMES

Identification of clinical and pathological and radiological factors to predict risk for

resectability in non metastatic carcinoma rectum.

SAMPLE SIZE CALCULATION

$n = (4*p*q)/ (d^2)$

where,

p = proportion of recurrence (60%),

q=1-p (1-0.60),

d=10%

Sample size= 144

SAMPLING :

For all patients with a newly diagnosed rectal cancer, a pretreatment staging evaluation is required, which includes all patients who are diagnosed with carcinoma are discussed in the Multidisciplinary Tumor Board Meeting and their treatment plan is decided. Treatment plan may include surgical resection or non-surgical management. However, some patients after the treatment plan is made choose to continue further treatment at their local hospital and hence discontinue further treatment at our Hospital. Patients who had received surgical intervention elsewhere but have presented at our Hospital for further management are also discussed in the Multidisciplinary Tumor Board Meeting, however since they had received treatment else where they were excluded from the study.

ANALYSIS:

Categorical variables weresummarized using counts and percentages. Quantitative variables were a using mean and standard deviation or median and IQR. Prevalence of stiffness will be presented with 95% CI. Chi square test will be used to compare the categorical variables between need and no need of surgery. Two sample t-test / Mann Whitney U test (depending on normality) will be used to compare the continuous variables between need and no need of surgery. The risk factors /predictors will be determined using logistic regression and the estimate of effect will be given as Odds ratio(95% CI).

VARIABLES :

- Age
- Sex
- Body Mass Index (BMI)
- Duration of symptoms
- Mobility of the tumour
- Obstruction of the tumour
- Histological classification of the tumour
- Tumour stage (based on MRI)
- Nodal involvement (based on MRI)

- Circumferential Resection Margin (CRM)
- EMVI (Extramural venous invasion)
- Tumour Regression grade (TRG).

The study includes :

- History and physical examination.
- Routine laboratory tests, including liver function tests , radiological imaging (CT, MRI)
- Histopathology report after the pathologist has examined the final resection specimen. The "y" prefix is used for those cancers that are classified on the basis of a surgical specimen after neoadjuvant pretreatment (e.g., ypTNM). The designation of the clinical stage of a rectal cancer generally rests upon the diagnostic biopsy, physical examination, and radiographic studies, such as computed tomography (CT), MRI, and transrectal ultrasound. An important point is that pathologic T stage (pT) entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category.

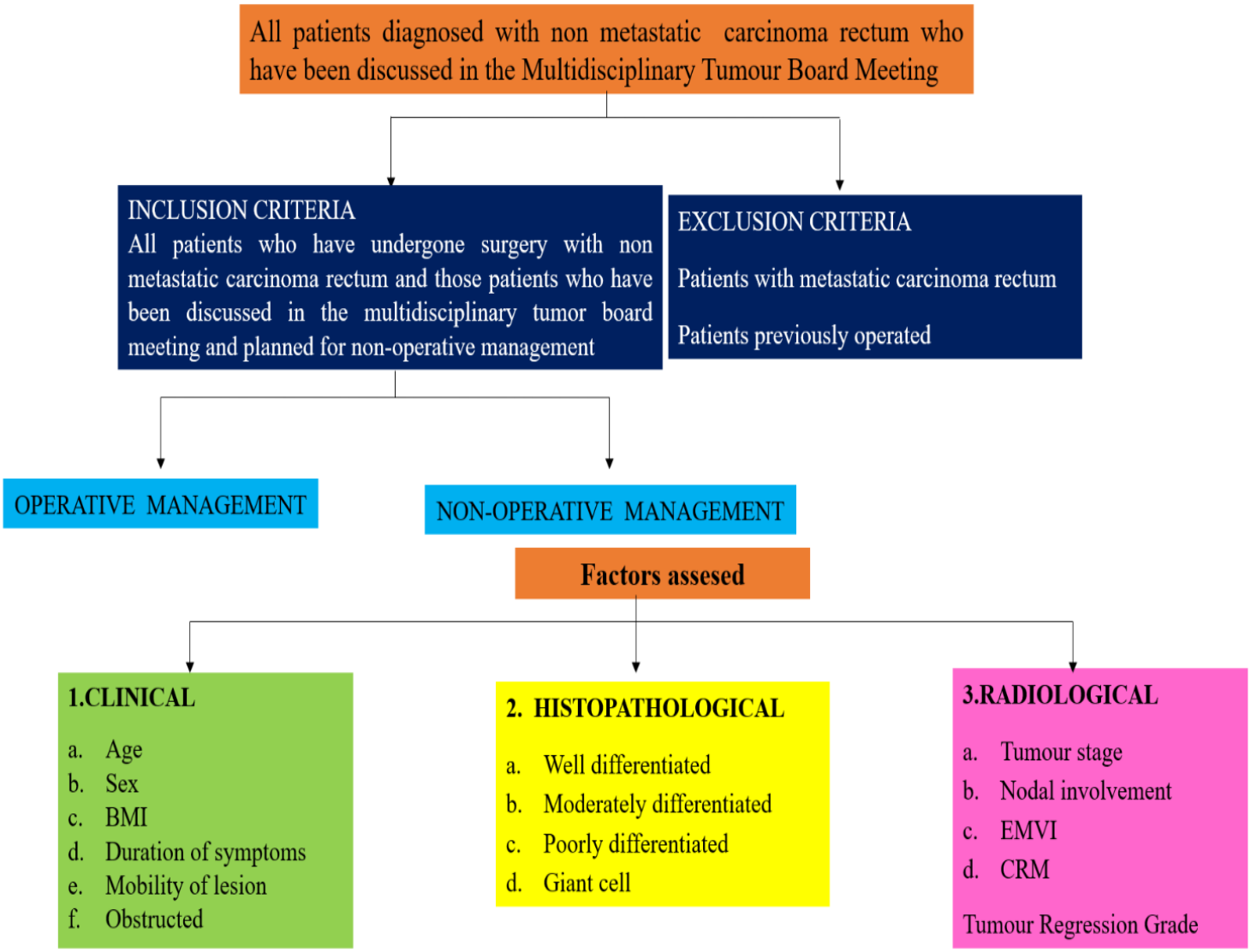
After evaluation of newly diagnosed rectal carcinoma, all patients are discussed in Multidisciplinary Tumor Board Meeting and treatment plan is made. In this study we have included patients with non-metastatic carcinoma rectum both who were managed operatively and non-operatively and have attempted to analyze the factors which predict resectability in these patients.

Statistical analysis

All statistical analysis was done using Stata version 13.1. Descriptive statistics like frequencies, percentage and median were used to represent demographic and clinical variables . Associations and correlations between demographic data, variables and selected outcome were done using chi square test and pearson correlation test.

OUTLINE OF THE STUDY

Figure 1


All patients diagnosed with non metastatic carcinoma rectum who have been discussed in the Multidisciplinary Tumour Board Meeting
INCLUSION CRITERIA
All patients who have undergone surgery with non metastatic carcinoma rectum and those patients who have been discussed in the multidisciplinary tumor board meeting and planned for non-operative management
EXCLUSION CRITERIA
Patients with metastatic carcinoma rectum
Patients previously operated
OPERATIVE MANAGEMENT
NON-OPERATIVE MANAGEMENT
Factors assesed
1.CLINICAL
a. Age
b. Sex
c. BMI
d. Duration of symptoms
e. Mobility of lesion
f. Obstructed
2. HISTOPATHOLOGICAL
a. Well differentiated
b. Moderately differentiated
c. Poorly differentiated
d. Giant cell
3.RADIOLOGICAL
a. Tumour stage
b. Nodal involvement
c. EMVI
d. CRM
Tumour Regression Grade

RESULTS

There were 144 patients included in the study. 90 were in the study arm (underwent surgery) and 54 in the control arm (did not undergo surgery)

1. DEMOGRAPHIC DETAILS

AGE:

The median age was 52 years old, 21 being the youngest and 76 being the oldest. Median age in the operated group was 52yrs and inoperable group was 48yrs . This was statistically not significant (p=0.0829)

It was noted that out of the 90 patients who underwent surgery 78% of the patients were over 40 years. It was also noted that out of the 54 patients who did not undergo surgery 92% of the patients were over 40 years of age.

Table-2 Age distribution

AGE (years)	DISTRIBUTION IN OPERATED PATIENTS	PERCENTAGE IN IN OPERABLE PATIENTS
20-40	22.0 %	7.9 %
40 - 60	41.6 %	54.4 %
>60	36.4 %	37.6 %

GENDER:

There was a male predominance overall, males 90 (62.5 %) and females 54 (37.5 %) . There was no significant gender difference between operated (61 % male, 39 % female) and non operated (64 % male, 36 % female)patients (p= 0.6612).

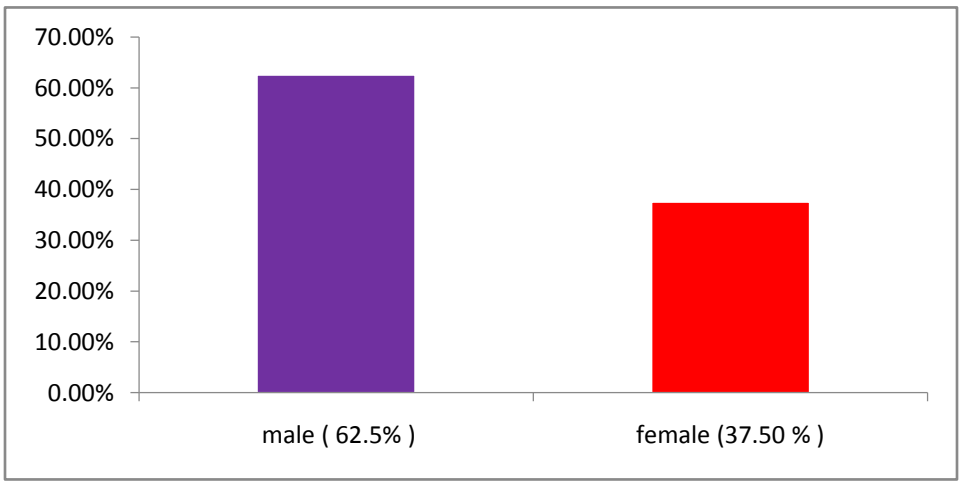


Figure-2 Sex ratio

2. BODY MASS INDEX (BMI)

Out of the 144 patients, BMI was not recorded in 26 patients who were all among the inoperable patients. The distribution of cases with documented BMI based on WHO classification is as follows.

RANGE OF BMI	OPERATED PATIENTS (%)	IN OPERABLEPATIENTS (%)
Underweight (< 18.5)	16	28.57
Normal (18.5 – 24.9)	54	35.7
Pre obese (25 – 29.9)	26	21.4
Obese class I (30 – 34.9)	4	14.2
Obese class II (35 – 39.9)	0	0
Obese class III (> 40)	0	0

Table-3 BMI

The Mean BMI in the operated group 22.8 and in the inoperable group was 21.4which was statistically significant(p=0.0001).

3. **DURATION OF SYMPTOMS :**

Out of the 144 cases, duration was not mentioned in 5 cases. In the operated cases, 77.78 % of the patients had presented within one year of onset of symptoms . Only 5 patients (5.6 %) had symptoms longer than 2 years duration in this group. In the inoperable group it was noted that of the 50 cases with documented duration, 16 patients (32 %) had presented within one year of onset of symptoms while 22 patients (44 %) had symptoms for one to two years and 12 patients (24 %) had symptoms for longer than 2 years. The duration of symptoms was found to vary significantly between the two groups(p=0.000365).

Table-4 Duration of symptoms

DURATION	OPERATED PATIENTS	INOPERABLEPATIENTS
< 1 year	77.78 %	32 %
1 – 2 years	16.7 %	44 %
> 2 years	5.6 %	24 %

4. MOBILITY OF THE LESION :

In the operated patients out of 90 patients , in 23 patients the mobility was noT mentioned either in view of high lesion or due to poor documentation. Of the remaining cases, 42 patients (46.1 %) had mobile lesions and 25 patients (29.2 %) had lesions with restricted mobility.In the inoperable group of patients it was noted that out o 54 patients, 25 patients did not have documentation on mobility due to high lesion or poor documentation. Out of the remaining cases, 7 patients (12.9 %) had mobile lesions while 22 patients (40.7 %) had lesions with restricted mobility which attained statistical significance(p= 0.000522).

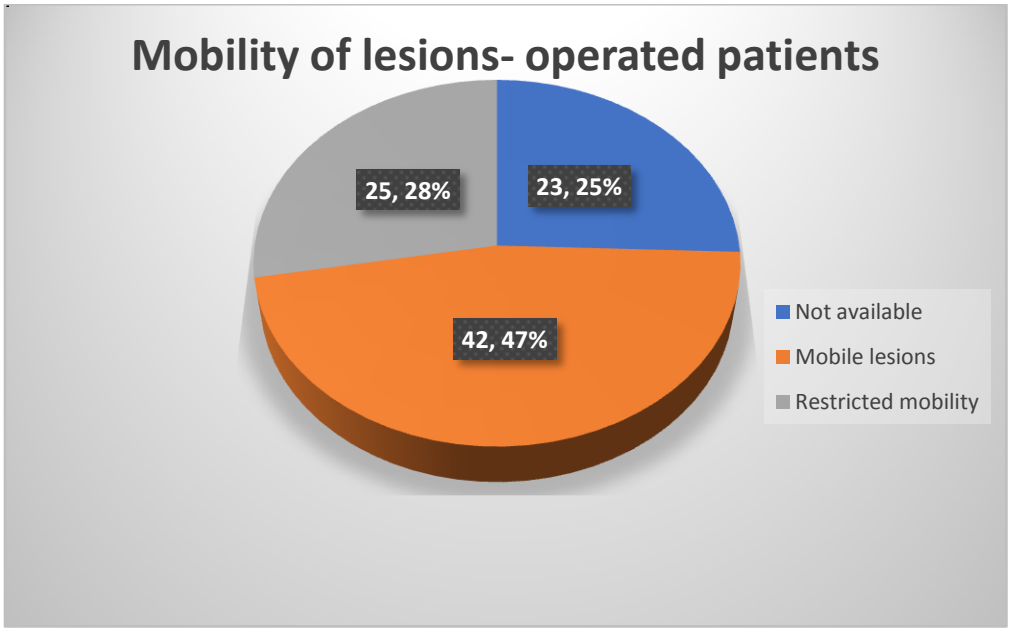


Figure 3- Mobility of lesions in operated patients

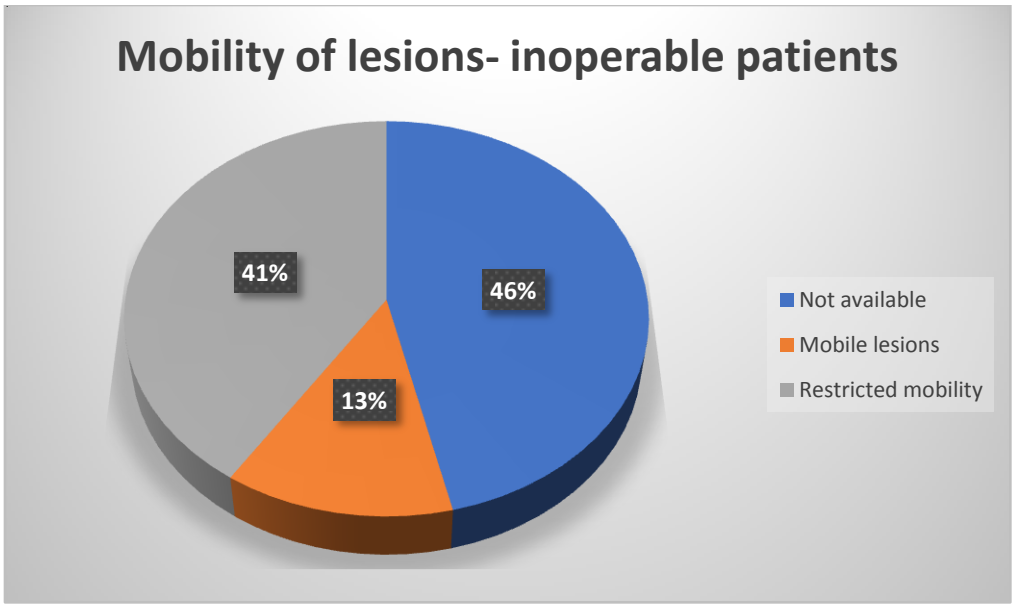


Figure 4- Mobility of lesions in inoperable patients

5. OBSTRUCTION OF THE TUMOUR :

Of the 90 operated patients, in 23 patients (27 %) the level of obstruction was not mentioned due to high lesion or poor documentation. 30 patients (37.7 %)had no obstruction while 39 patients (42.86 %) had obstructed lesion. In the inoperablepatients,14 patients (25.92 %) did not have the required details due to above mentioned reason. 8 patients (14.81 %) had non obstructed lesion and 32 patients (59.2 %) hadobstructed lesion. Higher level of obstruction was seen in the inoperable group (p=0.01316).

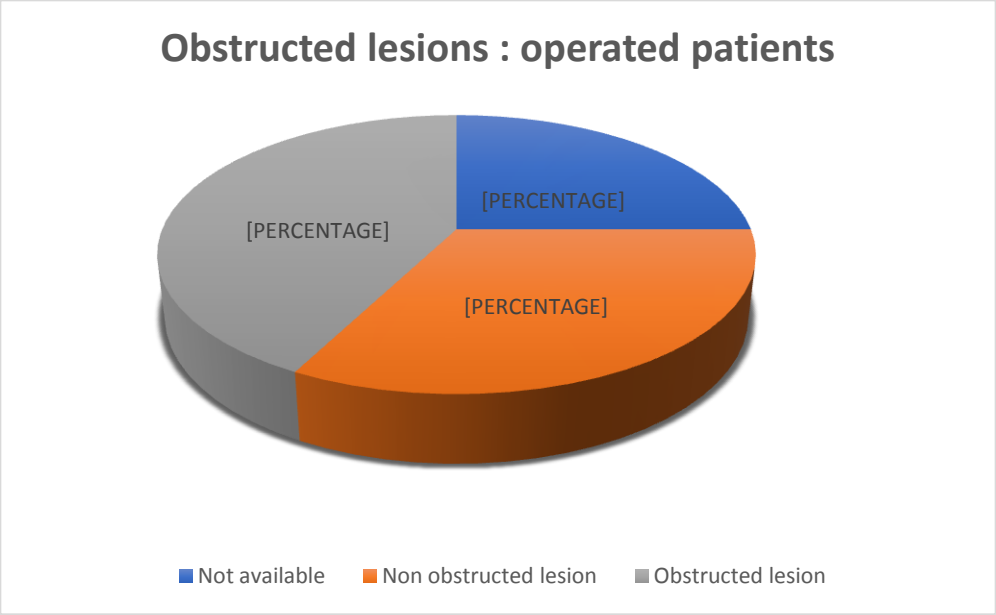


Figure 5- Obstruction of tumor in operated patients

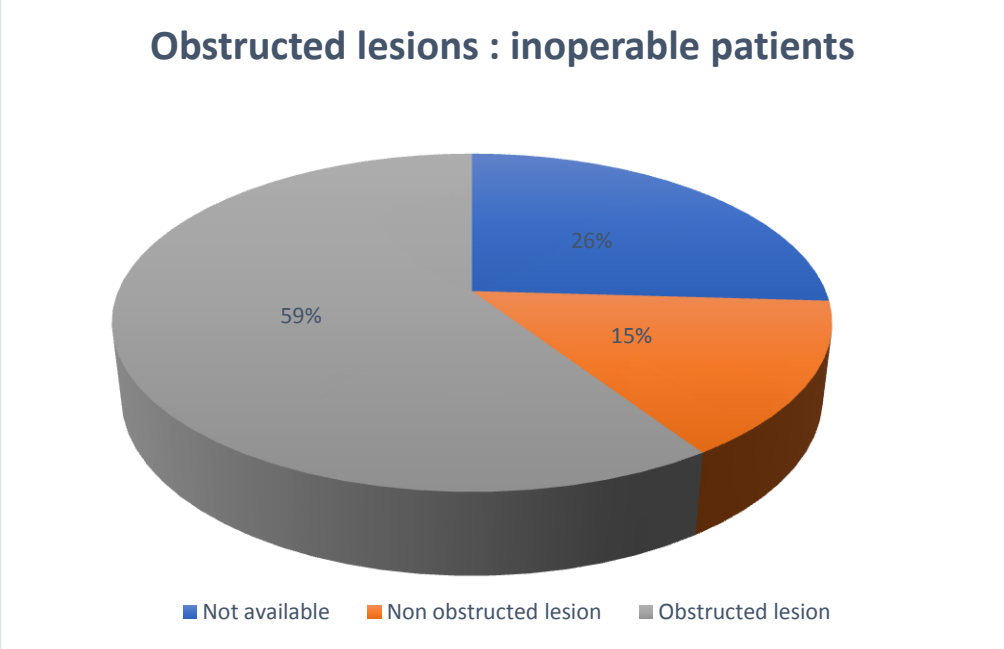


Figure 6- Obstruction of tumor in in operable patients

6. HISTOPATHOLOGY :

Of all the 90 operated patients , majority of the patients had moderately differentiated adenocarcinoma (81.8 %). The other main group consisted of poorly differentiated adenocarcinoma (15.56 %). There was only one case of well differentiated adenocarcinoma (1%) and one case of no residual tumour (1 %).Of the inoperable cases the histopathology consisted of 72.2 % cases with moderately differentiated adenocarcinoma and 27.7 % cases with poorly differentiated adenocarcinoma. Inoperable group had a significantly higher number of patients with poorly differentiated adenocarcinoma (p= 0.0405).

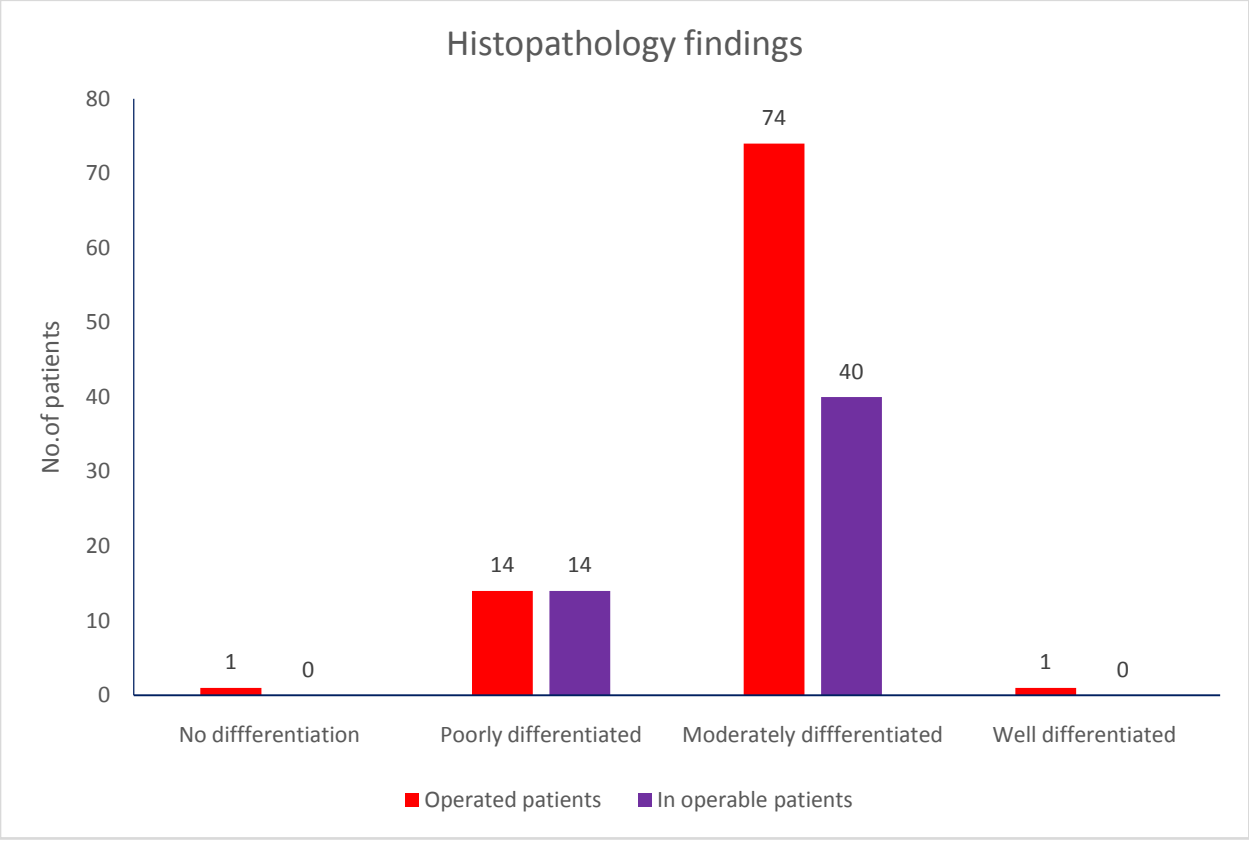


Figure 7- Histopathology findings

7. RADIOLOGICAL FEATURES :

The radiological features that were studied included Circumferential Resection Margin (CRM), Extramural venous invasion (EMVI), nodal stage, tumour stage and tumour regression grade (TRG).

8. CIRCUMFERENTIAL RESECTION MARGIN (CRM)

In the operated patients, 48 % patients had CRM positive. In the inoperable patients 79 % patients had CRM positive which was significant (p= 0.000005). There were 4 patients in the inoperablegroup who did not have CRM reported.

9. EXRAMURAL VENOUS INVASION (EMVI)

In the operated patients , 44 % patients had EMVI positive. Whereas in inoperablepatients there were 72 % patients with positiveEMVI (p=0.00006).

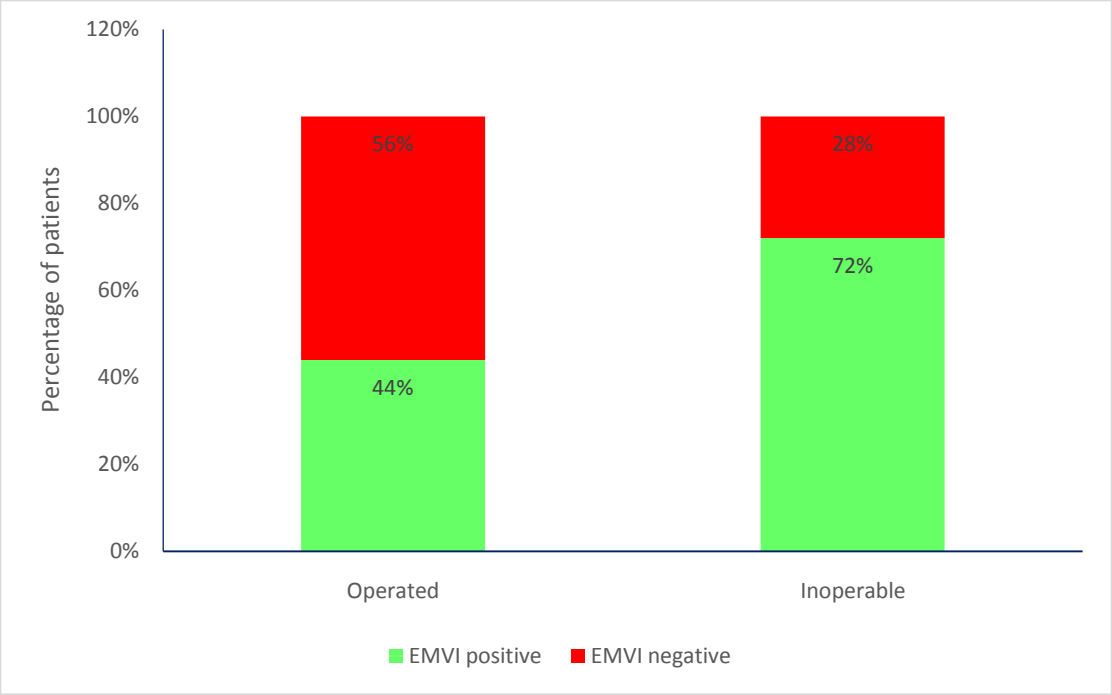


Figure 8- EMVI status in operated and inoperable patients

10. NODAL INVOLVEMENT :

In operated group , 86.67 % of the patients had nodal involvement. In the inoperablegroup , 89.12 % of the patients had nodal involvement.It was also noted that in the operated group, 17.78 % of cases had involvement of CRM, EMVI and nodal involvement and 41.8 % of inoperablegroup had involvement of all three above mentioned factors (p=0.6634).

11. TUMOUR STAGE :

In operated group, 7.68 % of patients had T2 stage, 64 % had T3 stage and 28.56 % of patients had T4 stage. In theinoperablegroup, 2.9 % had T2 stage, 18.9 % had T3 stage and 78.2 % had T4 stage which was significantly higher than the prevalence T4 stage tumours among operated patients (p=0.01).

TUMOUR STAGE	OPERATED (%)	INOPERABLE (%)
T1	0	0
T2	7.68	2.9
T3	64	18.9
T4	28.56	78.2

Table 5- Tumor staging between operated and inoperable patients

12. TUMOUR REGRESSION GRADE (TRG) :

In operated patients, 5.26 % of patients had TRG 1, 22.36 % had TRG 2, 40.79 % had TRG 3 (most common), 23.69 % had TRG 4, 1 % had TRG 5 and 7.8 % patients did not have follow up imaging , hence values were not documented.

Of the 54 patients in the inoperablegroup only 23 patients had follow up imaging of which 9.84 % had TRG 3, 62% had TRG 2, 28.1% had TRG 1.

DISCUSSION

The primary outcome we aimed to achieve was to identify clinical , pathological and radiological factors to predict risk for resectability in non metastatic carcinoma rectum.The secondary outcome we aimed to achieve was to predict the probable treatment process to the patients at an early stage. Thus helping the patients to be better informed regarding their treatment plan . The various variables assessed are discussed below to help determine those specific variables that can help formulate the treatment plan earlier than the current practice.

AGE

Based on literature it is noted that Carcinoma rectum is more common above 50 years of age(4) Similarly in this study it was noted that 78% patients above the age of 40 had resectable tumours

whereas 92 % of patients with non resectable tumours were abov the age of 40. Odds ratio is 0.31with 95 % confidence interval (0.13 to 0.73).

SEX

Male predominance is noted in rectal carcinoma. In our study it was also noted that there was a male predominance (62.5 %). There was no significant difference between the sex distribution in resectable and non resectable cases. However it was seen that in less than 30 years there were more number of female patients (74 % in operated group and 81 % in the inoperable group).

BODY MASS INDEX

There is a lot of epidemiological evidence that obesity is associated with an increased risk of colorectal cancer(41). This is mainly due to insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation which are all involved in carcinogenesis and cancer progression . However in his study it was noted that the patients were predominantly under normal weight category as per WHO classification(42). It was noted that there were many underweight patients both in the resectable (16%) and non resectable groups (28.57 %). This was attributed to patients with obstructing lesions and poor nutrition. It was also noted that there were significantly more patients in the obese class I group among the patients with non resectable tumours (14.2 %) when compared to resectable tumour group (4%). Odds ratio in these patients with class I obesity is 0.25 (Confidence interval 0.08 – 0.79).

DURATION OF SYMPTOMS

It was noted that patients with longer duration of symptoms had a higher risk of non resectable tumours(8). In this study, the odds ratio for patients with symptoms for more than 2 years to have non resectatble tumour was 5.32 (confidence interval 2.02- 14.02).

MOBILITY OF TUMOUR

Restricted mobility fixed tumour is suggestive of locally advanced tumour. The staging or these patients is only complete after imaging. However based on literature it is seen that these patients usually require multimodality treatment (neo adjuvant therapy) so that R0 resection can be done. Similarly in this study it was noted that there was a higher chance on non respectability and multimodality treatment in patients with fixed lesions. The limitation in this study included the non documentation of mobility in 48 cases of the total 144cases.

OBSTRUCTION OF THE TUMOUR

As mentioned earlier the limitation of this study includes non documentation for 37 patients regarding obstruction of the tumour. However similar to literature, patients with restricted

mobility and obstructed lesion were more common in locally advanced tumour which required multimodality management and were more likely to be unresectable. Odds ratio for a patient with obstructed tumour to be unresectable based on this study is 1.88 (Confidence Interval 1.07 – 3.29).

HISTOPATHOLOGY :

As mentioned in literature, moderately differentiated carcinoma is the most common. Similarly in this study it was noted that moderately differentiated carcinoma was more common. However it was noted that poorly differentiated carcinoma was more common in the inoperable group (27.7 %) than in the operated group (15.56 %).

CIRCUMERENTIAL RESECTION MARGIN (CRM)

CRM assessed in this study is based on the pre treatment MRI (staging MRI) . It is seen that an involved CRM is associated with increased local recurrence, distant metastasis and poor overall survival(43)(19). Similarly in this study it was noted that in non resectable patients 79 % had CRM involved compared to 48 % patients with resectable tumours with involved CRM . The odds ratio of patient with involved CRM to have non resectable tumour is 4.08 (Confidence interval 2.19 – 7.58).

It has been identified that certain variables identified during pre operative assessment have a worse prognosis requiring multimodality treatment. These include T3 tumors with extramural extension >5 mm, or N2 disease, the presence of extramural vascular invasion or potential

CRM involvement. Similarly in our study it was noted that patients with T4 disease, nodal involvement ,EMVI positive and CRM positive had significantly higher chance of inoperability or need or multimodality treatment(44).

EXTRAMURAL VENOUS INVASION (EMVI)

Extramural venous invasion (EMVI) is defined as the presence of tumor cells within blood vessels beyond the muscularis propria. EMVI is an independent factor for poor prognosis in rectal cancer, with the sensitivity of 28.2–62% and specificity of 88–94%(45). In this study as well it was noted that of the resectable tumour group 44 % patients had EMVI involved , whereas in the non resectable group 72 % patients had EMVI involved. The odds ratio for a patient with EMVI positive to have non resectable tumour is 3.27 (Confidence interval 1.82 – 5.9).

Extramural tumor extension is an established independent prognostic factors of rectal carcinoma. Study has showen that patients with tumors with an extramural extension of 5 mm or less, regardless of the nodal status, have a 5-year cancer-specific survival rate of 85%, whereas in tumors with extramural extension greater than 5 mm, the survival rate is 54%(46). In our study as well it was noted that there is a significant adverse correlation between EMVI and rectal cancer.

NODAL INVOLVEMENT

Based on literature it is noted that higher level of nodal involvement is directly related to worse prognosis and non respectability of tumour. Similarly in this study it was noted that 89.12% of non resectable tumours had lymph node involvement. However it was also noted that there was 86.67 % resectable patients with nodal involvement, these patients underwent neoadjuvant therapy prior to their surgery .

TUMOUR STAGE

As multiple studies show that higher the tumour staging (T3 T4) higher the chance of local or distant spread of the malignancy(47). Similarly in this study it was noted that 78.2 % of patients with non resectable disease had T4 disease and 18.9% patients had T3 disease(48). However in patients with resectable tumour it was seen that only 28.56 % had T4 disease and 64 % had T3 disease. The patients with T3 disease were given multimodality treatment with neoadjuvant chemoradiation thus downstaging the disease prior to surgery. The patients in this group with obstructed tumours underwent diversion procedure prior to neoadjuvant treatment.

Table -5: Comparison of tumor stage between operated and inoperablepatients.

TUMOUR STAGE	OPERATED (%)	INOPERABLE (%)
T1	0	0
T2	7.68	2.9
T3	q	18.9
T4	28.56	78.2

12. TUMOUR REGRESSION GRADE (TRG) :

Tumor regression grading (TRG) system aims to categorize the amount of regressive changes after cytotoxic treatment(37)(39) . It usually refers to the amount of therapy induced fibrosis in relation to residual tumor or the estimated percentage of residual tumor in relation to the previoustumor site.The commonly used grading for rectal carcinoma includes Dworak and Rodel system(38). In this study , Rodel system was used. The limitation of this variable was that there was follow up MRI for patients with resectable tumours hence the data could be analysed, however, in non resectable group there only 31 patients out of 54 patients had follow up MRI.The other 23 patients had either continued treatment elsewhere or were on palliative treatment.

In resectable group most common TRG was TRG 3 (40.79 %). In the non resectable group out of the 31 patients 62 % had TRG 2 and 28.1% had TRG 1.

Dworak et al	**Rodel et al**
0. No regression	0. No regression
1. Predominantly tumor with significant fibrosis and/or vasculopathy	1. Regression of <25%

2. Predominantly fibrosis with scattered tumor cells (slightly recognizable histologically)	2. Regression of 25–50%
3. Only scattered tumor cells in the space of fibrosis with/without acellular mucin	3. Regression of >50%
4. No vital tumor cells detectable	4. Complete regression

Table -6:Tumor regression grade

	VARIABLES	OPERABLE (90)	INOPERABLE (54)	P VALUE
1	AGE (MEDIUM)	52	47	0.0829
2	GENDER (MALE)	61	64	0.6612
3	BMI (MEAN)	22.8	21.4	0.0001
4	DURATION OF SYMPTOMS (>2 YEARS)	5	13	0.000365
5	MOBILITY (FIXED)	25	22	0.000522
6	OBSTRUCTION OF TUMOUR (OBSTRUCTED)	39	32	0.013167
7	HISTOPATHOLOGY (POORLY DIFFERENTIATED ADENOCARCINOMA)	16	28	0.040524
8	CRM	48	79	0.000005
9	EMVI	44	72	0.00006
10	LYMPHADENOPATHY	87	89	0.663422
11	TUMOUR STAGE (T4)	25	42	0.01

Table 7: Summary of results

CONCLUSION

This study was planned to identify factors that predict resectability in non metastatic carcinoma rectum. The important conclusions from this study are :

- Rectal carcinoma is more common after 40 years of age, however the age does not help in predicting if the tumour is resectable.
- Resectability cannot be predicted based on the sex of the individual.
- Though studies show obesityis a risk factor for non resectable tumours, this study could not establish a significant correlation regarding the same. It was noted that there were more underweight patients in the non resectable group, probably owing to long duration of symptoms, obstruction and poor nutrition.
- If the duration of symptoms is longer than 2 years there is a significant chance of the tumour being non resectable.
- Although other studies have shown that the risk of non resectability is higher if the growth is obstructed or has restricted
- Mobility, this could not be proved in this study due to small numbers
- Moderately differentiated carcinoma was the most common histopathological type of tumour. There was a higher number of poorly differentiated adencarcinoma in the non resectable group, however it wasn't significant to predict that patients with poorly differentiated adenocarcinoma have higher chance of having non resectable tumours.
- Circumferential Resection Margin (CRM) is an important predictor of resectability as seen in other studies. In this study also it was found to be significantly higher in non resectable tumour group and in patients receiving neoadjuvant chemoradiation. So it can

be used as a valuable predictor while making the treatment plan for a patient with non metastatic rectal carcinoma.

- Extramural Venous Invasion (EMVI) is also an important predictor of respectability based on other studies. In this study it proved to be a valuable indicator of non resectability and for patients requiring multimodality treatment.
- Nodal involvement is considered as an important predictor of resectability. However in this study there was no significant difference between the resectable and non resectable groups. In the resectable group , patients with lymph node involvement underwent multimodality treatment.
- In tumour staging it is known that higher the T stage the higher the chance of nonresectability. Similarly in our study it was noted that patients with T4 disease had a significantly higher risk of having non resectable tumour.mobility. This fact is shown in other studies, however could not be proved in this study since there were many cases were the details were not documented.
- Moderately differentiated carcinoma was the most common histopathological type of tumour. There was a higher number of poorly differentiated adencarcinoma in the non resectable group, however it wasn't significant to predict that patients with poorly differentiated adenocarcinoma have higher chance of having non resectable tumours.
- Circumferential Resection Margin (CRM) is an important predictor of resectability as seen in other studies. In this study also it was found to be significantly higher in non resectable tumour group and in patients receiving neoadjuvant chemoradiation. So it can be used as a valuable predictor while making the treatment plan for a patient with non metastatic rectal carcinoma.

- Extramural Venous Invasion (EMVI) is also an important predictor of respectability based on other studies. In this study it proved to be a valuable indicator of nonresectability and for patients requiring multimodality treatment.
- Nodal involvement is considered as an important predictor of resectability. However in this study there was no significant difference between the resectable and non resectable groups. In the resectable group , patients with lymph node involvement underwent multimodality treatment.
- In tumour staging it is known that higher the T stage the higher the chance of non resectability. Similarly in our study it was noted that patients with T4 disease had a significantly higher risk of having non resectable tumour.
- Based on studies , lower the Tumour Regression Grade, higher the risk of non resectability. However, in this study we were unable to prove the same due to poor follow up MRI in the non resectable group.

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November 08, 2019

Dr. Evangeline Preeti Jennifer,
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Department of General Surgery,
Christian Medical College,
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Sub: **Fluid Research Grant: New Proposal:**
Identification of predictors for resectability in non-metastatic carcinoma rectum.
Dr. Evangeline Preeti Jennifer (Emp. No. 29456, General Surgery, Dr. Mark Ranjan Jesudason (emp. No. 28081), Surgery-II, Dr. Rajat Raghunath (emp. No. 28850), Surgery, Ms. Gowri, Biostatistics.

Ref: IRB Min. No. 11217 [OBSERV] dated 05.03.2018

Dear Dr. Evangeline Preeti Jennifer,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Identification of predictors for resectability in non-metastatic carcinoma rectum" on March 05, 2018.

The Committee reviewed the following documents:

1. IRB application format
2. Cvs of Drs. Evengeline, Mark Ranjan J, Rajat.
3. Waiver of Consent Form,
4. No. of documents 1- 3.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on March 05th 2018 in the Jacob Chandy Hall, Paul Brand Building, Christian Medical College, Vellore 632 004.

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Name	Qualification	Designation	Affiliation
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Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr.Min(Clinical Counseling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
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Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor, Endocrinology, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
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Dr. John Antony Jude Prakash	MBBS, MD	Professor, Clinical Microbiology, CMC, Vellore.	Internal, Clinician.
Dr. AjithSivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.23.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Identification of predictors for resectability in non-metastatic carcinoma rectum" on a monthly basis. Please send copies of this to the Research Office(research@cmcvellore.ac.in).

With best wishes

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

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