COLORECTAL CARCINOMA IN HOSPITAL KUALA TERENGGANU FROM 1987 TO 1999

BY

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Dissertation Submitted In Partial Fulfillment Of
The Requirement For
The Degree of Master of Medicine
(General Surgery)

UNIVERSITI SAINS MALAYSIA

YEAR 2002

II . ABSTRACT

Background : Colorectal carcinoma is one of the most common malignant neoplasm in this country . Its incidence is rising . New development in genetic studies has brought better understanding of colorectal carcinoma . Newer treatment option has increased survival and quality of life . However the impact of this development has not been fully utilized especially in the rural areas in this country .

Objective : To study the epidemiology of colorectal carcinoma in the Kuala Terengganu Hospital and the state of Terengganu . To determine the clinical presentation of colorectal carcinoma in this hospital and to evaluate the mode of investigation and treatment received by the patients with colorectal carcinoma . The primary objective is to assess the treatment outcome in terms of recurrence and survival .

Methods : Between 1987 to 1999 , 90 patients were treated in Hospital Kuala Terengganu for colorectal carcinoma . The sex , age , duration of symptom , the main and subsequent presenting problems , the type of special investigation and the location of the tumour were determined from patients record . Type of surgery , method of resection and presence of metastases were noted at the time of surgery . Specimens were sent to the pathologist for assessment of the tumour grade .

Survival duration were obtained from the patients record . 2 year survival rate was assessed and factors affecting survival were determined using nonparametric statistical analysis .

Result : There was almost equal sex distribution among the patients . 53% of the patients were more then 60 years and young colorectal carcinoma consist of 6 % . Median duration of symptom was 4.3 months . 43.3 % of the patients presented with intestinal obstruction and a almost equal number of them underwent emergency surgery . 68.7 % of the patients were in Duke's C and D at presentation . At the time of presentation 24.4 % already had liver metastases . 30 day mortality and morbidity was 2.2 % and 11.1 % respectively . Overall survival was 37.8 % . Statistically Duke's staging , stage of metastases , initial clinical presentation , type of operation and use of adjuvant therapy significantly influences($p < 0.05$) the 2 year survival in this study .

Conclusion : In this study , late presentation of colorectal carcinoma was common . Duke' s staging , initial clinical presentation , type of operation and the use of chemotherapy influences survival . A better follow up of colorectal carcinoma patient is needed .

III ABSTRAK

Latar Belakang : Kancer kolon dan rektum adalah salah satu ketumbuhan malignan yang utama di negara ini . Kini insiden kanser in sedang meningkat . Kefahaman kita berkenaan penyakit kanser kolon dan rectum bertambah dengan perkembangan terbaru dalam bidang genetic. Kaedah perubatan yang terbaru membolehkan survival dan kualiti hidup ditingkatkan . Walaubagaimanapun perkembangan ini tidak dipergunakan sepenuhnya terutama di kawasan pendalaman di negara ini .

Objektif : Kajian in bertujuan untuk mengetahui epidemiologi penyakit kanser kolon dan rectum di Hospital Kuala Terengganu dan di negeri Terengganu . Kajian ini juga melihat pada riwayat clinical penyakit ini dan menilai cara penyiasatan dan rawatan yang diterima oleh pesakit penyakit kanser kolon dan rectum . Objektif utama ialah untuk mengetahui kadar survival dan rekuren .

Tatacara : Di antara tahun 1987 dan 1990 , seramai 90 pesakit kanser kolon dan rectum telah dirawat di Hospital Kuala Terengganu . Jantina , umur , jangkamasa gejala , riwayat penyakit yang utama , jenis penyiasatan yang digunakan dan lokasi kanser dipastikan melalui rekod pesakit . Jenis pembedahan , cara pembedahan dan metastasis tumor pada masa pembedahan dicatitkan .

Pengradan tumor oleh pakar patologi juga dicatitkan . Jangkamasa pesakit hidup selepas pembedahan didapatkan melalui rekod pesakit . Kadar survival 2 tahun dikira dan faktor – faktor yang mempengaruhinya dipastikan melalui pengiraan statistik .

Keputusan : Distribusi jantina dikalangan penyakit adalah hampir sama rata . 53 % pesakit berumur 53 tahun keatas dan 6 % adalah pesakit di bawah 40 tahun . Kadar median jangkamasa gejala adalah 4.3 bulan . 43.3 % pesakit datang dengan keadaan usus tersumbat dan jumlah yang sama menjalani pembedahan kecemasan . Semasa kali pertama pesakit dinilai , 68.7 % dari mereka berada dalam peringkat Dukes' C dan D . Pada masa yang sama 24.4 % dari mereka sudah mempunyai metastasis di hepar . Kadar mortaliti dalam 30 hari dan mobiliti adalah 2.2 % dan 11/1 % masing-masing . Kadar survival keseluruhan adalah 37.8 % . Klasifikasi Dukes' , peringkat metastasis ,gejala utama , jenis pembedahan dan pemberian terapi adjuvan mempengaruhi kadar survival dalam masa 2 tahun di dalam kajian ini .

Kesimpulan : Dalam kajian ini pesakit kanser kolon dan rektum hanya datang untuk rawatan apabila penyakit mereka sudah merebak . Klasifikasi Dukes' , peringkat metastasis ,gejala utama , jenis pembedahan dan pemberian terapi adjuvant mempengaruhi kadar survival .Cara yang lebih baik diperlukan untuk mengikuti pesakit yang sudah menjalani rawatan .

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VII ACKNOWLEDGEMENT

I wish to express my gratitude and appreaciation to my supervisors Datuk Jamil Abdullah from the Department of Surgery Hospital Kuala Terengganu and Dr Myint Tun from the Department of Surgery Hospital Universiti Sains Malaysia , for their guidance and supervision in the preparation of this dissertation . I thank them for the valuable time they spent with me to put through this study .

I also wish to thank my Head of Department , Associate Professor Dr. Abdul Hamid , for his suggestions and support .

I wish to thank all the lecturers in Hospital Universiti Sains Malaysia , clinical specialists from Hospital Kuala Terengganu and my colleagues for their encouragement and support

In Malaysia more and more cases of colorectal carcinoma are being identified and treated . With establishment of a colorectal unit in Hospital Selayang and Hospital Universiti Kebangsaan Malaysia , proper research can be done on the Malaysian population in relation to colorectal carcinoma . As this country is a multiracial society , the differences in colorectal carcinoma within races may exist . This may be compounded with different levels of development in various parts of the country .

This dissertation is a retrospective study of patients with colorectal carcinomas seen in Hospital Kuala Terengganu , Kuala Terengganu from 1987 to 1999 . This hospital is a tertiary referral center serving the rural population of Terengganu state in the east coast of peninsular Malaysia. This study will assess the presentation and outcome of treatment of colorectal carcinoma in a general hospital where there is no specialized colorectal unit . From here we will know how to improve the service for the benefit of patients in the treatment of colorectal carcinoma .

2.0 LITERATURE REVIEW

2.1 EPIDEMIOLOGY

Colorectal carcinoma is the fourth commonest form of cancer occurring world-wide , with an estimated 783,000 new cases diagnosed in 1990 . It affects men and women equally. World-wide , colorectal carcinoma represents 9.4 % of all incident cancer in men and 10.1 % in women (3) . However it is not equally common throughout the world .If the western countries (North America ; Northern , southern and western Europe ; Australia ; New Zealand) are combined , colorectal cancer represents 12.6 % of man and 14.1 % of women of all incident cancers . Elsewhere colorectal cancer represents 7.7 % and 7.9 % of all incident cases in men and women respectively (3).

Different populations worldwide experience different levels of colorectal cancer , and these levels change with time . Population living in one community also experience different levels of colorectal cancers (4).

Groups of migrants quickly lose the risk associated with their original home community and acquire the patterns of the new community , often starting within one generation of arrival(4).

Ethnic and racial differences in colorectal cancer suggest that environmental factors play a major part in the etiology of the disease . In Israel male Jews born in Europe or the United States are at a higher risk of colon cancer compared to those born in Asia or Africa . Incidence in the offsprings now approaches or surpasses that in white people in the same population and is three or four times higher than Japanese in Japan . For these reason colorectal cancer is widely believed to be an " environmental " disease (4) .

The incidence of colorectal carcinoma is a rising trend(5) . The incidence of colorectal cancer in eastern part of the Netherlands (700,000 inhabitants) was determined for two years, 1981 and 1996. In 1981 the diagnosis of colorectal cancer was seen in 232 patients in this region and in 1996, it was seen in 410 patients. The population remained almost stable during this time. Therefore, the incidence rose from 33 to 55 per 100,000 inhabitants from 1981 to 1996, respectively. In 1981, 25 percent of the carcinomas were proximal (to the sigmoid colon); this increased to 37 percent in 1996. The location of the tumour is also more proximal now (6) .

A similar trend is also observed in Bulgaria . It showed the incidence rate of colorectal carcinoma from 1985 to 1998 increased steadily from 22.14/100,000 to 37.18/100,000 (an increment of 15.04/100,000) . Most of the patients in this study (60 %) were diagnosed at a later stage of the disease and this trend continues to 1998 (7) .

In Malaysia a similar trend is observed .Data from the ministry of health shows an increase of colorectal carcinoma rate from 8.1 % (1973 cases) in 1987 to 11.9 % (4215 cases in 1995 . Colorectal cancer was the third commonest cancer death in Malaysia from 1987 to 1995 (8).

Rectal cancer is slightly more common in men, whereas there is a slight predominance of colon cancer in women(1). An American has approximately a 5 percent probability of developing colorectal cancer during a 70-year life span. Most cases of colorectal cancer are diagnosed in patients over the age of 50, and the incidence of the disease rises steadily after that age. Despite clear relationship with aging, colorectal cancer is not strictly a disease of the elderly and between 6 to 8 percent of cases occur in individuals under the age of 40(1). In the Far East ,the incidence of colorectal carcinoma is more in younger population compared to Western countries (9).

In a retrospective study in Egypt , 38 % of the colorectal cases were below the age of 40 years old. The onset of familial and hereditary forms of the disease occurs at a much earlier age, typically around the third decade (10).

There are few studies in assessing the awareness of colorectal carcinoma in an adult population . On assessment of public awareness of colorectal carcinoma , it was found that even in countries with high literacy rate only a minority (11 %) were aware of colorectal screening (11) .

Similarly Nadel et al noted only 22.9 % of Americans aged more than 50 years old had gone for screening for colorectal carcinoma (12) .

2.2 : ETIOLOGY AND RISK FACTORS

2.2.1 : Diet

Evidence from epidemiological studies seems to show consistently that intake of dietary fat and meat is positively related to the risk of colorectal cancer . This evidence was obtained from ecological studies , animal experiments , and case control and cohort studies (13).

In 1990 Willett et al published the results from the United States nurse health study involving a follow-up of 888,751 women aged 34 – 59 years who were without cancer or inflammatory bowel disease at recruitment . After adjustment for total energy intake , consumption of animal fat was found to be associated with increased risk of colon cancer. No association was found with vegetable fat . The relative risk in women who ate beef , pork , or lamb as a main dish every day was 2.49 compared with women reporting consumption less than once a month . The authors suggested that intake of animal fat increases the risk of colon cancer (13) . In the Asian population a similar trend could be found . Zhang et al (2002) in a study involving a rural region in China found that meat intake and saturated fat were prominent risk factors for colorectal carcinoma (14).

Dietary fiber has been proposed as accounting for differences in the rates of colorectal cancer between Africa and westernized countries – on the basis that increased intake of dietary fiber may increase faecal bulk and reduce transit time . Many studies found no protective effect of fiber in cereals but have consistently found a protective effect of fiber in vegetables and fruits (13 , 14).

Folate deficiency enhances intestinal carcinogenesis in several animal models. An increasing number of epidemiologic studies indicate that higher intakes of folate either from dietary sources or from supplements may lower the risk of colorectal adenoma and cancer(15). More limited data also suggest that dietary methionine, which might also influence methylation, may have a similar protective role. High alcohol consumption, which has a strong antifolate effect, also has been related to higher risk of colorectal neoplasia. The deleterious effects of alcohol are accentuated when folate or methionine intake is low (15).

2.2.2 : Physical activity , body mass index , and energy intake

Evidence from epidemiological studies show that men with high occupational or recreational physical activity seem to have a decreased risk of colon cancer. Giovannucci et al reported that activities from moderate intensity such as brisk walking is associated inversely with the risk of large adenoma (16).However there is no evidence to show a consistent association

between obesity and the risk of colorectal cancer .

2.2.3 : Hormone replacement therapy

Increasing evidence supports an association between hormone replacement therapy and a reduced risk of colorectal cancer . The risk is halved with 5 – 10 years of use . Whether this association is casual or is associated with some other factor is not known (17).

2.2.4 : Familial risk factors

A family history of colorectal polyps is associated with increased risk of colorectal carcinoma in other family members . However 80 % of patients have " sporadic " colorectal carcinoma, with no familial risk factor identified. First degree relatives of patients with colorectal carcinoma are at a high risk to develop colorectal neoplasia . Orrom WJ et al(1990) , studied colonoscopic finding in patients with colorectal carcinoma and found that 21 % of them had neoplastic disease and another 28 % had adenoma beyond the splenic flexure(19) . 25 % of these patients who were positive for adenoma are below 40 years old(19) . Kesani et al (2002) reported 44 % patients under 40 years old in their study had family history of colorectal carcinoma and these patients usually presents with more advanced stage of disease (18) .

- Polyposis syndrome

Familial syndrome takes the form of familial adenomatous polyposis syndromes (FAP) . FAP accounts about 0.5 % of all colonic carcinoma . It is autosomal dominant inherited propensity to develop numerous adenomas throughout the colon , some of which in time will become malignant (2) . The polyp appears at puberty and nearly all patients will have polyp by the early thirties .

- Hereditary non polyposis colonic carcinoma (HNPCC)

This is more common but less obvious than FAP and is autosomal dominant inheritance . It is clinically similar to that of sporadic cases but more common in younger age groups . Lynch (1996) classified HNPCC into 2 subtypes ; site specific colon cancer where individuals of a family are susceptible to colonic cancer but not cancers of other organs (Lynch type 1) ; cancer family syndrome where female members of the family are prone to breast and uterine cancer as well as colonic cancer (Lynch type 2) . The cancers occur predominantly on the right side of the colon and are of low malignancy in contrast to sporadic cases (20).

2.2.5 : Molecular Genetics

Colorectal adenoma carcinoma sequence

One of the most important concepts in colorectal carcinoma to emerge in recent years has been the adenoma – carcinoma sequence , a term that describes the stepwise progression from normal to dysplastic epithelium to carcinoma associated with the accumulation of multiple clonally selected genetic alterations.

Although the adenoma – carcinoma sequence has not been proven directly , there is considerable indirect evidence to support it from a range of epidemiological , clinical , histopathological and genetic studies .

1. Epidemiological and clinico-pathological evidence – age distribution curves for adenoma and carcinoma show that the prevalence of both increases with increasing age , but adenomas are recognized and their prevalence peaks at least 5 years earlier than that of colorectal carcinomas (21). In surgical resection specimens and during endoscopic examination adenomas are found to coexist with carcinoma in about 30 % of cases and patients who have colorectal carcinoma and simultaneous adenomas have been shown to have increased risk of synchronous and metachronous carcinoma (22).

The anatomical distribution of adenomas and carcinoma is similar , occurring more frequently distal to splenic flexure ; adenoma of left colon often contain more severe dysplasia or invasive adenocarcinoma (23).
Finally endoscopic removal of adenomatous polyps appear to reduce the long term risk of colorectal carcinoma (24).

2. Genetic evidence – the concept of carcinoma arising from genetic abnormality has existed for many years . In colorectal carcinoma , the genes of interest that are involved in genetic alterations may be classified into three types : oncogenes , tumour suppressor genes and DNA repair genes (25). In 1990 Fearon and Vogelstein proposed a genetic model for colorectal tumorigenesis (26) . This model postulated that mutational activation of oncogenes , coupled with mutational inactivation of tumour suppressor genes , leads to the development of colorectal tumours . Although these alterations occur in sequence , it is the total accumulation of changes which is important . The key oncogene in this model was *ras* and the key tumour suppressor genes were proposed residing on chromosome 5q , 17p , and 18q . However , now there is an alternative pathway in a subset of colorectal tumours that less frequently involves the above mentioned genes and often involves mismatched repair genes(26,27)

- Adenomatous Polyposis coli (APC) -is one mutation known to occur early in the adenoma – carcinoma sequence affects the adenomatous polyposis coli (APC) tumour suppressor gene located on chromosome 5q21 .

Mutation of this gene is responsible for familial adenomatous polyposis (FAP) , an autosomal dominant disorder characterized by development of thousands of colorectal adenomas appearing in adolescence or early adulthood (28). If untreated it leads to colorectal carcinoma at the third or fourth decade of life . APC mutation or allelic losses of 5q are observed in 40 – 80 % of colorectal carcinomas and are found at a similar frequency in adenomas (29) .

- K-*ras* – Activating mutation of the oncogene K-*ras* also occurs early in the adenoma – carcinoma sequence . This gene is involved in signal transduction of regulatory pathways critical for normal proliferation and differentiation (30) .

Activating K-*ras* mutation occurs in 35 – 42 % of colorectal carcinoma and were also observed at similar frequency in large adenomas . It is also being investigated as a potential predictors of metachronous adenomas (29 , 32).

- P53 – located on the short arm of chromosome 17 , p53 was initially implicated in colorectal carcinoma as a result of the frequent loss of 17p in allelic loss and cytogenic studies . It functions as a sequence specific DNA binding protein and transcription factor controlling the expression of a large number of genes (29 , 33). It has been labeled as the guardian of the genome because of its ability to block cell proliferation in the presence of DNA damage , to stimulate DNA repair and to promote apoptotic cell death if repair is insufficient . The alteration in p53 or 17p allelic loss has been reported to occur in 50 – 75 % of adenocarcinoma and in 4 – 26 % of adenoma (29 ,31) .

- 18q loss - this is the second most common region of allelic loss in colorectal carcinoma occurring in about 70 % of cases . 18q loss is also observed in 10 – 30 % of early adenomas and it is raised to 60 % in late adenomas . The original tumour suppressor gene in this region was thought to be the " deleted in colorectal cancer " (29 , 31 , 34).

Microsatellite instability

A recently proposed alternative pathway for a subset of colorectal tumours is characterized by the presence of microsatellite instability (MSI).
Microsatellite are a type of DNA that consists of tandem repeats , usually between one and five base pairs , repeated many times (35).
Hundreds of thousands of microsatellites are found interspersed throughout the human genome and are particularly prone to errors during DNA replication .
Such errors are usually repaired by mismatch repair (MMR) proteins but , in the absence of competent MMR function , microsatellite error accumulates . When these errors are sufficiently frequent , the term MSI or replication error positive is applied .
Thus MSI can be interpreted as a marker for a state of hypermutability (36,37).
MSI is observed in almost all adenocarcinomas from patients with hereditary non – polyposis colorectal cancer (HNPCC) that occurs in 10 – 15 % of sporadic colorectal carcinoma (38). The presence of MSI in sporadic colorectal carcinoma and HNPCC correlates significantly with a number of clinical and pathological features including proximal location , diploid DNA content , a favourable Dukes' staging , improved survival and the presence of a Crohn's like inflammatory infiltrate (38 , 39 , 42) .

The presence of MSI has a favorable genetic prognostic markers for colorectal carcinoma and may imply an increased risk of a second primary tumour in the colon or an endometrial tumour in the patient or family members .

In the future this genetic testing will come into common use for the prognosis of colorectal carcinoma and will affect their management (40 , 41).

2.3 : CLINICAL PRESENTATION

Patients with colonic and rectal carcinoma have a broad range of clinical presentation that can be sub-classified according to the anatomic site of the primary . In the earliest stage they may be asymptomatic . Caecal and right sided tumours accounts for 20 % of large bowel carcinoma , 70 % occur distal to the splenic flexure , and about 45 % are at or below the recto-sigmoid junction (1,2). Kullavanijaya (2002) in a retrospective analysis reported distal colorectal carcinoma was about 72 % (45) . However there is a shift from left sided toward right sided carcinoma confirmed by epidemiological study by Cucino et al (44). Bowel habit change , weight loss and mucous bloody diarrhea are the most common presentations(45).

Caecal and right sided carcinoma

Right sided tumours are often remarkably silent and many patients present with only the symptom and signs of iron deficiency from protracted occult blood loss .Preoperative anaemia was the most common finding with right sided tumour present in 58 % of patients (46) . As the lumen becomes narrowed the patient complains of intermittent colic , centrally or in the right iliac fossa , which is often post-prandial , stimulated by gastro-colic reflex .

Typical distal ileal obstruction occurs if the tumour blocks the ileo-caecal valve causing incompetence of the valve characterized by progressive central abdominal colicky pain , faeculent vomiting and abdominal distension . Not infrequently a palpable mass may be the presenting symptom .

Patients can occasionally present with acute appendicitis when the carcinoma occludes the appendicular orifice and produce acute inflammation or from a perforated carcinoma .

The tumour may penetrate the bowel wall , producing a sealed perforation and formation of abscess on the psoas muscle which may manifest as painful right iliac fossa mass (2).

Left sided and sigmoid colon

Patients commonly present with change of bowel habit , often constipation alternating with diarrhea , usually accompanied by lower abdominal colicky pain . The symptoms progressively become worse and later patients may develop obstruction .

Change in bowel habit is often accompanied by passage of altered blood , sometimes mucus , in the stool or on its surface .

Occasionally they may present as frank per-rectal bleeding which is usually intermittent and brisk .

A few patients may have localized left iliac fossa pain associated with a palpable mass . At the splenic flexure presence of tumour must be distinguished from a palpable left kidney .

Some patients have few symptoms until they present with intestinal obstruction . If the ileo-caecal valve is incompetent the obstructed large bowel decompresses into the small bowel and produces a mixed picture of small and large bowel obstruction .

If the ileo-caecal valve is competent , the caecum will be distended and this will lead to perforation . Occasionally the tumour itself can perforate and present as diffuse peritonitis . Perforation of colon associated with malignancy is reported to be between 3 – 8 % (43) .

At times the tumour may become attached to the adjacent organ such as lateral abdominal wall , uterus , bladder and vagina . The tumour may perforate the organs and present as a fistula . Colonic carcinoma is the second most common cause of colovesical fistula after diverticular disease (1 , 2).

Rectal carcinoma

Most patients with rectal carcinoma present with per-rectal bleeding and change of bowel habits . The blood may be dark in color , mixed with stool or bright red separate from the stool . For this reason patients attribute it to hemorrhoid, a symptom produced by advanced rectal tumour (1,2).
The patients also may have tenesmus and spurious diarrhea .

Penetration of tumour to the sacrum will produce perineal pain shooting down the thigh . Intestinal obstruction is a late sign , indicating advanced disease (1).
Metastatic symptoms from colorectal carcinoma are rare presentations .

2.4 PATHOLOGY

The vast majority of colorectal carcinomas are adenocarcinoma . They may be well differentiated (20 %) , moderately differentiated (60 %) or poorly differentiated (20 %) . The epithelial cells lining the glands show nuclear stratification , pleomorphism , hyperchromasia and high mitotic rate (47). If large amount of mucin is produced by the tumour and more then 70 % of the tumour is occupied by mucin lakes , it is classified as a mucinous carcinoma (47).

Lee YS(1988) in a study of large bowel carcinoma in Singapore noted that non mucinous carcinoma is by far the commonest histological type (74.7 %) followed by mucinous carcinoma (20.7 %) . Other histological type were relatively uncommon (48). They include carcinoid tumours (1.8 %) , signet ring cell carcinoma (1.5 %) , squamous cell carcinoma (0.7 %) , undifferentiated carcinoma (0.4 %) and adenosquamous carcinoma (0.2 %) . The proportion of mucinous carcinoma was greatest among the Malay and Indian (48). The right colon had a greater proportions of poorly differentiated carcinoma than the left colon (48 , 49 , 50) . This tendency is more evident in the female . Mucinous carcinoma occurs more frequent in younger age group and in populations with with low risk for colorectal carcinoma (48 , 49 , 50). A greater proportion of mucinous carcinoma located in the rectum and right colon (48 , 49 , 50). Mucinous carcinoma usually present in more advanced stage and have a low curative resection rate (49). The overall survival rate of patients with mucinous carcinoma is worse than that of non-mucinous carcinoma (48 , 49 , 50) .

2.5 : STAGING

Several staging methods are in use throughout the world, and each has its own strengths and weaknesses. The most commonly used are Duke's classification, American Joint Committee on Cancer (AJCC) and the Union Internationale Contre Cancer (UICC) TNM classification. Based on AJCC/UICC , several variations developed but the most commonly used is pathological (pTNM) staging (51 , 52).

Dukes' classification introduced in 1929, has the advantage of simplicity but it lacks precision. It does not reflect accurately the depth of tumour penetration, the extent of spread outside the bowel wall, the number of lymph nodes involved and the presence or absence of metastases.

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Staging gives information about prognosis in general, but particularly indicates the probability of occult hepatic metastases, which is the major factor affecting survival.

Table 1:

Dukes' Classification

A	Intramucosal
B	Tumour involving the bowel wall
C	Regional lymph node involvement(lymph nodes around the superior and inferior mesenteric vessels ; excluding para-aortic nodes)
D	Adjacent organs or distant metastasis(including para-aortic nodes)

Table: 2

AJCC/UICC TNM pathologic staging, 1997 version

Primary tumour (T)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in-situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the sub serosa, or non peritonealized pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures, and/or perforates visceral peritoneum

Regional Lymph Node

NX	Regional Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N3	Metastasis in four or more regional lymph nodes

Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table: 3

Stage Grouping

AJCC/UICC				Dukes'
Stage 0	Tis	N0	M0	
Stage 1	T1	N0	M0	A
	T2	N0	M0	
Stage 2	T3	N0	M0	B
	T4	N0	M0	
Stage 3	Any T	N1	M0	C
	Any T	N2	M0	
Stage 4	Any T	Any T	M1	D

Table: 4

Common ' T stage ' penetration

Colon – Transverse , Sigmoid , Recto-sigmoid

pT1 invasive into submucosa
pT2 muscularis propria
pT3 through the muscle , not through serosa
pT4 through the mucosa
pT4 into contiguous organ

Extra-peritoneum rectum

pT1 Invasive into the submucosa
pT2 Muscularis propria
pT3 Transmural into peri-rectal fat
pT4 Into contigous organ

For this dissertation Duke's Classification was used as the staging system .