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Colorectal Carcinoma in the Young

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1. Introduction

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract. In the United States, it is the third most commonly diagnosed cancer, next only to breast and lung. It is the second most common cause of cancer-related death both in the USA and in the UK. (www. cancer. org, O'Connell et. al. 2004^a, Leff et. al. 2007). Its incidence has risen rapidly in Asia to pose a problem (Yuen et. al. 1997, Huang et. al. 1999, Mohandas et. al. 1999, Yiu et. al. 2004, Goh et. al. 2005, Gupta et. al. 2010). Sung et. al. (2005) in a review on CRC in Asia stated that many Asian countries, e. g., China, Japan, South Korea, Singapore have experienced an increase of two to four times in CRC incidence during the past few decades. In Hong-Kong CRC is the second most common cancer and the third most common cause of cancer death (Yuen et. al. 1997). Tamura et. al. (1996) in a Japanese study reported that age adjusted incidence for CRC per 100,000 population were 12. 6 and 8. 7 for males and females respectively in 1974, 20 and 13. 6 in 1980, 42. 5 and 25. 6 in 1991. Bae et. al. (2002) estimated on the basis of Korean data, that the expected number of cancer deaths in Korea showed an increasing trend for CRC, although the same did not hold for all cancers. In Iran, age adjusted CRC incidence per 100,000 population per year increased from 1. 61 in 1970-80 to 4. 2 in 1990-2000 in men and 2. 35 to 2. 72 for women (Hosseini et. al. 2004). The rising trend is more striking in affluent than in poorer societies and differs substantially amongst ethnic groups. Changes in dietary habits and lifestyle are recognized causes. Genetic characteristics of a population mediate the effect of life style change into disease propensity (Lin et. al. 2010). Although the common perception is that it is a disease of an older person, there have been many reports from different parts of the world on CRC in the young adults (Bulow 1980, Denmark; Ohman 1982, Sweden; Jarvinen and Turunen 1984, Finland; Ibrahim and Karim 1986, Lebanon; Adloff et. al. 1986, France; Isbister and Fraser 1990, New Zealand; Yuen et. al. 1997, Hong-Kong; Fante et. al. 1997, Italy; Ashenafi 2000, Ethiopia; deSilva et. al. 2000, Srilanka; Paraf and Jothy 2000, Canada; Turkiewicz et. al. , 2001, Australia; Singh et. al. 2002^a, Nepal; Kam et. al. 2004, Malayasia; Frizis et. al. 2004, Greece; Guraya and Eltinay 2006, Saudi Arabia; Fazeli et. al. 2007, Iran; Karsten et. al. 2008, USA; Gupta et. al. 2010, India). O'Connell et. al. (2004^a) have reviewed the literature. The proportion of patients in the young group in a population of CRC patients was significantly larger in reports from Asia and Africa, as compared to the Western reports.

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The definition of 'Young adults' varies, to a small extent, in the literature. Majority of articles defined 'young' as <40 years, although upper limits of 50 years, 35 years and 30 years have also been used. O'Connell et. al. (2004^a) estimated the average value of incidence of CRC in the young adults (<40 years) in the population of all CRC patients as 7% and adjusted it to 6%, when outliers were removed. It has been suggested (Hamilton 2005) that the adjustment was 'too small' and a more realistic estimate was an average of 2.2%. Leff et. al. (2007) gave an estimate of 2-3%. About 0.1% of all CRC patients were diagnosed <20 years of age, ~1% between 20-34 years, ~4% between 35-44 years and a further ~12% between 45-54 years. These average figures reflect the extent of the problem in the West. The figures from Asian and African countries are considerably higher, a quarter or a half of a study group of CRC patients may belong to the under-40 group (Ashenafi 2000, Ethiopia; deSilva et. al. 2000, Sri Lanka; Singh et. al. 2002^a, Nepal; Guraya and Eltinay 2006, Saudi Arabia; Gupta et. al. 2010, India). Numerical values given later will establish that the problem of CRC in the young adult in the developing world is alarming.

We now cite reports, from the West (USA, France, Scotland) and from Asia (Iran, Hong Kong), in which the incidence of the disease amongst the young adults has been studied in the same population over a period of time. O'Connell et. al. (2003) noted that in the USA, colon cancer incidence in older patients (60+ years) remained stable in the period 1973-1999 while rectal cancer incidence decreased by 11%. In the group of younger patients (20-40 years) colon cancer incidence increased by 17%, while rectal cancer incidence rose by 75% in the period 1973-1999. The improvement in the older age group is a reflection of more efficient cancer screening in the USA, a result of improved awareness of the disease. It is possible that relative ignorance about the problem of CRC in the young adult is responsible for the fact that the problem has worsened over the years. Other issues namely difference in molecular genetics, may also be present. In Iran, Hosseini et. al. (2004) defined the younger group as <60 years, compared figures in two 10 year periods 1970-1980 and 1990-2000 and found an increased proportion of <60 years CRC patients (in a population of all CRC patients) in the latter decade, 37.5% as against 70%. An increase in proportion of the young CRC patients was noted over a prolonged time span. Mitry et. al. (2001) from France reported that below-45 age standardized incidence rates doubled in the period 1976-1982 and then again in the period 1983-1989, in both genders and stabilized thereafter. In Hong-Kong, the overall incidence in >50 years group increased at a rate of 4% a year during 1978-87, whereas in Scotland a higher overall incidence remained stable during this period (Yuen et. al. 1997).

O'Connell et. al. (2004^b) in a study of American patients found that young (20-40 years) colon cancer patients tend to have later-stage and higher-grade tumours. However they have equivalent or better 5 year cancer-specific survival compared to 60+ older group, an apparently paradoxical result. Although most reports agree on a more severe advanced disease at presentation in the young (Adloff et. al. 1986, Cusack et. al. 1996, Nath et. al. , 2009) and many also agree with the opinion that prognosis is not poorer in the young (Jarvinen and Turunen 1984, Turkiewicz et. al. 2001, Karsten et. al. 2008) some reports (Moore et. al. 1984, Adkins et. al. 1987, Okuno et. al. 1987, Singh et. al. 2002^a) do not share the view that prognosis is 'equivalent or better'. In spite of this difference in assessment, a favourable prognosis in many studies should inspire more aggressive detection and treatment for the young.

The genetic basis of CRC has been investigated in recent years. A satisfactory understanding of the disease, tumour characteristics, relationship of disease susceptibility with age and issues related to survival rely on an understanding of the link between molecular genetics and disease. A complete resolution of this relation is a tall order, but a modest beginning is

being made. Intelligent choice of treatment protocol, surgical as well as chemotherapeutic is also influenced by research on molecular genetics of CRC (Liang and Church 2010). Hereditary CRC usually occurs at a relatively young age, between 25 and 55 years in individuals with family history of CRC. Individuals who inherit the predisposing cancer gene have a greater chance of developing the disease (Murday and Slock 1989, Lynch et. al. 1991, Lynch and de la Chapelle 2003, Ewart Toland, 2012). The importance of family history in determining susceptibility to CRC in the young has been stressed in the literature (St. John et. al. 1993, Fuchs et. al. 1994, Turkiewicz et. al. 2001). There exist literature reports that identify genetic factors in younger CRC patients which differ from those in older patients and may be responsible for greater cancer susceptibility of the younger patients (Farrington et. al. 1998, Chan et. al. 1999, Morris et. al. 2007, Berg et. al. 2010, Lin et. al. 2010).

In this essay, we focus on the issue of CRC in young age, with particular reference to developing countries. The relative incidence figures of CRC in the young patients as compared to older patients in different parts of the world are given. These figures, in greater detail are given in the Indian context (section 2). Disease stage at presentation and tumour characteristics of younger patients, often in comparison with the older ones in different countries are then summarized (section 3). A brief reference to de novo cancer in Asians (section 4) is followed by a discussion of some recent genetic studies in the young (section 5). Section 6 contains a discussion on predisposing factors and section 7 has focus on prognosis in the young. The paper concludes (section 8) with a brief reference to the effect of recent molecular genetic research on treatment protocol.

2. Incidence amongst young adults

The relative incidence of CRC in the younger group varies significantly from one country to another. As cited above, it is typically 2-3% in the West. Other European figures are: Fante et. al. (Italy): 1%; Endreseth et. al. (Norway):6%; Ohman (Sweden): 4%; Adloff et. al. (France): 3%; Yilmazlar et. al. (Turkey): 20%. The corresponding figures are much higher from several Asian and African countries: Nath et. al. (India): 35. 6%, <40 yrs; Gupta et. al. (India): 39%,<40 years; Singh et. al. (South Asia): 23%,<40 years (with a maximum incidence in 40-60 years, a decade earlier than Western figures): study period 1975-1981; Soliman et. al. (Egypt): 35. 6%,<40 yrs; Ashenafi (Ethiopia): mean age 47 years (61. 4% <50years, 36% <40 yrs,16% <30 yrs) in two 5 year periods with a 10 year gap; Guraya and Eltinay (Saudi Arabia): study period 1999-2004,63% <40 yrs, mean age 44years, peak incidence 30-39 years; Hosseini et. al. (Iran): 70% (<60 years):study period 1990-2000; Chew et. al. (Singapore):25% <40 years; Singh et. al. (Nepal): 28. 6% <40 years; de Silva et. al. (Sri Lanka): 19. 7% <40 years. Some of these references are detailed in Table 1. In Egypt, more than half of all CRC patients are below-50, patients under-30 constitute 22% of the population of all CRC patients (Soliman et. al. 1997). Qing et.al. (2003) in a comparative study of American and Chinese patients (1990-2000) reported that the mean age at diagnosis of 690 American patients was 69 years (20-91 years) and that of 870 Chinese patients was 48. 3 years (13-84 years); peak incidence was 70-79 years in Whites and 50-59 years in Orientals. The conclusion is that the Orientals are affected by the disease at a younger age. The same theme emerges from recent data from several Indian hospitals which includes our own recent work (Gupta et. al. 2010). In a period spanning 8 years (2000-2008), we found the ratio of under-40 to above- 40 years age group to be 0. 64. The study group comprised of 305 patients in SSKM Hospital, Kolkata, India, a premier referral Hospital. The values reported by three premier Oncology centers located in two cities in India and in another report by Pal (2006), based on work done

Sr. No.	Reference, Period of study	Age profile	Disease stage	Tumour characteristics
1	Lee 1968-91	62 patients, <40yrs	Dukes' A:8%, B:20%, C:23%, D:48%.	Half of stage D patients and 20% of lower stage patients (p=0.037) had high grade lesions.
2	Minardi, 1976-97	37 patients, <40yrs	Dukes' C:37%, D: 22%.	Mucinous tumour : 42%; moderate and poor differentiation : 84%
3	Cusack	186 patients, <40yrs	Dukes' C & D: 65.6%.	Poorly differentiated tumour in 41%, signet-ring cell tumours in 11.1%, infiltrating tumour leading edges in 69% of young patients. Aggressive tumour biology with higher frequency in <40yr patients (p<0.001), potentially metastatic.
4	Bedikian, 1944-1977	2609 patients, <50yrs age; 183 aged <40 yrs. Comparison between <30yr and 30-39yr age group and with yet older age group	96% of <40 years group had carcinoma extending beyond colonic wall.	Moderate and poorly differentiated neoplasms (80%) and mucinous variety (33%) in young.
5	Beckman 1943-1977	69 patients: 20-39yrs	67% Dukes' C and D	Mucinous variety (28%).
6	Varma	A review: all age groups	Advanced stage more frequent in the young.	Greater frequency of mucinous tumour in the young.
7	Cozart, Unusual Case Registry 1992-93	55 patients, <30yrs	62% Dukes' C and D	Poorly differentiated / mucinous variety: 33%
8	Howard	801 patients including <40yrs group	Advanced signs and stages more frequent in the young.	Greater frequency of mucinous variety in the young

9	Adkins, 1973-1984	705 patients; 45 patients, <35yrs	In the younger group: Dukes' A:2,B:8, C: 28, D: 7 patients.	19: poorly differentiated,19: well or moderately differentiated tumour
10	Moore, 1967-1981	3. 2% of 1909 patients <40yrs	Higher incidence of advanced disease, especially in second or third decades.	Greater incidence of mucinous variety (32. 3% in young vs. 8. 6% in the whole study group). Poorly differentiated tumour: 98%; distant metastases in one-third patients. Vascular (24%) and perineural (11%) invasion in the young.
11	Karsten. , 1998-2005	Younger group: 41 patients <40yrs Older group : >60 yrs	Advanced stage: T-3/4 lesion in 87. 8% of young/63% in older group (p=0. 002).	Poorly differentiated, (p=0. 003), mucin secreting/ signet ring (p=0. 005), more common in the young
12	Fairley, 1998-2001 Cancer Registry (NPCR,SEER)*	All age groups Young:20-49yrs	Less localized, more aggressive disease in terms of stage in the young (20-49yrs)	Incidence of poorly differentiated tumour in young (<50yrs) (i) twice as high as well differentiated ones in the young (ii)60% higher than that for well differentiated cancers in the old
13	Lichtman 1987-1991	57. 2% <70yrs	Dukes' C and D more frequent at a lower age (p=0. 03). Mean Age A/B-1 67. 7 yrs, B-2 70. 1yrs, C/D 63. 9yrs	Grade not related to age

14	Dozois, 1976-2002	1025 patients, <50yrs; Mean age 42. 4±6. 4 years 51% colon, 49% rectal (largest cohort of young-onset patients without genetic predisposition)	70% colon, 60% rectal: stage C&D	Colon Cancer: Mucinous(11%) & Signet cell (2%) Grade 2+3 for both rectum & colon cancer: ~87%
15	Behbehani 11 yrs period pre-1980	<40 years group: 56 patients	Advanced stage C&D: ~90% in young ~50% in general population	Poor differentiation: 21% in young, 8% in general population

*NPCR: National Program of Cancer Registries; SEER: Surveillance, Epidemiology and End Results

Table 1. Summary of references in the literature on stage and tumour characteristics in the USA

in the same referral hospital where Gupta et. al. (2010) worked are 0. 58, 0. 63, 0. 45, 0. 62. Average of these five ratios is 0. 52, which is equivalent to ~34% of < 40 years CRC patients amongst all CRC patients. This figure is of the same order as the values from several Asian and African countries cited above. They are also substantially larger than values recorded in National Cancer Registry (PBCR) in four Indian metropolises. The PBCR ratio is 0. 20 and has remained stable over 16 years (1988-2004).

The difference between PBCR values and those reported by five premier hospitals in India, irrespective of their location and specialty, cited by Gupta et. al. (2010) has a clear message. The concern and facilities for cancer detection in the premier hospitals is greater than those in district hospitals. The data of the district hospitals are reflected in the PBCR values. This is the reason for the larger proportion of under-40 patients reported by the premier hospitals. The reason for delay in diagnosis of a young patient in either the premier hospitals or the district hospitals, particularly in the developing world, is that unless there is a family history these patients are not screened. So cancers are usually symptomatic at presentation. Even when symptoms occur, they may initially be misdiagnosed. Rectal bleeding for example is often put down to an anorectal cause. O'Connell et. al. (2004^a) report an average delay in diagnosis of 6. 2 months, the reasons for which include a delay in presentation on the part of the patients, limited access to care and misdiagnosis on the part of the physician. This delay is larger in the developing world. Minimizing delay in diagnosis means not taking such symptoms lightly. Rectal bleeding usually has an anorectal cause, but when no such cause is obvious and the bleeding persists, colonoscopy is mandatory, regardless of patient's age. The same concern must apply to other less obvious symptoms.

In a review on CRC in Asia, Sung et. al. (2005) placed India at the bottom of the list amongst Asian countries, in order of decreasing CRC incidence. The data we provide does not contradict this assessment, but if relative incidence in the young is an indication, India has joined the rest of Asia.

3. Disease stage and tumour characteristics in the young adults

The most powerful predictor of outcome for young adults, as it is for older patients is disease stage. Two staging systems are in use and are cited in Table 1-3. One is the tumour-node-metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC). Microscopic extent of tumour invasion (T stage) and nodal involvement (N stage) from histological assessment are combined with assessment for metastatic disease (M stage) to specify a tumour stage. Brief description of TNM stages are: Tumour stages (T): Tumour in T1, invades submucosa, T2: invades muscularis propria, T3 and T4 are more extensive, T3 indicates invasion through muscularis propria into subserosa or into nonperitonealised pericolic or perirectal tissues while T-4 invades adjacent organs. Regional Lymph node stages: N1: 1-3 positive nodes, N2:4 or more positive nodes. Distant metastases stages (M): M1: Distant metastases present. The other classification system known as Dukes' system is: A: limited to bowel wall, B: penetration of bowel wall, C: lymph node involvement, D: distant metastatic disease present (Fry et. al. 2008).

Mucinous adenocarcinoma is one of the histological subtypes of colorectal cancers. It accounts for 5-15% of all primary CRC and is defined as a tumour with >50% of its body showing a mucinous pattern on histological examination and with a large amount of extra cellular mucin produced by secreting acini. This is distinct from signet ring adenocarcinoma, a rare variant in which mucin remains inside the cell, which is well known for its aggressiveness. It has been suggested that mucinous adenocarcinoma behaves differently from more common histological subtypes of CRC. However, its clinical implications remain unclear. According to published series, mucinous adenocarcinoma affects younger patients, is more frequent in proximal part of the colon and tends to present at a more advanced stage (Negri et. al. 2005).

In Table 1, 2 and 3 we tabulate data on disease stage and tumour characteristics, in particular its mucinous nature, of CRC patients in the USA (Table 1), in Europe, inclusive of Turkey and the UK and Australia (Table 2) and in Asia and Africa (Table 3).

Several reports cited in Table 1 (Sr No 1,2,3,5,7,9,14) were entirely on features of CRC in the younger patients. In several other reports (Sr No. 4,6,8,10-13,15), both the younger and the older patient groups were studied and comparative features were assessed. The size of the younger group was mostly ~50, was ~200 in two reports (Sr No 3 and 4) and was 1025 in the work of Dozois et. al. (2005) (Sr no 14), the largest cohort of young CRC patients. In reports that included older and younger patients, older patients were much larger in number (Sr No 4,8-10). In all studies that were on younger patients alone, a high incidence of advanced stage (C+D: >70%) was reported. In studies that included both groups, the frequency of advanced disease in the young was as high or higher (Sr No. 4,11,15). In all of them, advanced disease stages were found to be more frequent in the young than in the old. In studies on younger patients alone, a significant proportion of patients had aggressive lesions, namely mucinous, poorly differentiated tumours with infiltrating leading edge. The frequency of aggressive tumour biology varied from one study to another but remained significant in all of them. In the comparative studies (Sr No. 6,8,10-12,15), the younger patients showed a higher frequency of aggressive tumour biology. Only one report (Sr No. 13) concluded that grade was not related to age.

Country	Sr No.	Reference, Period of study	Age profile	Disease stage	Tumour characteristics
France	1	Adloff 1973-1980	1037 patients; 3% <40yrs	No significant difference in stage between <40 and >40 Yrs group.	Greater frequency of mucinous and poorly differentiated carcinoma in the young
Finland	2	Jarvinen 1970-1979	249 patients, <40yrs	53% Dukes' C and D.	Premalignant condition more common in young
Greece	3	Frizis 1994-2003	Two groups: 11 young <40yrs; 45 old > 80 yrs.	Dukes' C 54. 5% in the young and 44. 4% in the elderly group.	Undifferentiated tumour: 36. 3% of the young and 8. 8% of elderly.
Sweden	4	Ohman 1950-1979	48/1061 patients are <40 years (21-39 years)	Dukes' A same proportion in young and old, Dukes' B fewer, Dukes' C more in young	
Norway	5	Endreseth 1993-1999	2283 patients with rectal cancer <70 years, <45 yrs: 132, 45-49 yrs: 153 50-69 yrs:1998	Dukes' C&D : under 45: 73/132(~55%) 45-69yrs: 998/2152(~46%)	Higher frequency of poorly differentiated tumours (27 vs. 15%) & N-2 stage (37 vs. 15%) with distant metastases (38 vs. 20%); 56% of under-40 years: developed metastases (20-26% of older group) after tumour resection
	6	Berg 2010	181 patients, 45 of them < 50 yrs	Dukes' C &D 54% in < 50 yrs group 46% in 51-70 yrs 36% in > 70 yrs	

Country	Sr No.	Reference, Period of study	Age profile	Disease stage	Tumour characteristics
UK	7	Leff 1982-1992	49 patients all < 40 yrs: 67% in 31-40 yrs, 2 in their teens	Among all patients: 60% Dukes' C&D. Among patients at risk (family history /predisposing factor): 56% Dukes' C	Among all patients: 59% moderately & 22% poorly differentiated . Among patients at risk: 53% moderately & 20% poorly differentiated
Italy	8	Fante 1984-1992	Three groups <40, 41-50, 51-55 years: ~1%, 6%, 6% of 1298 patients	Stage did not differ	Histological features did not differ
Turkey	9	Yilmazlar 1986-1993	237 patients; 46 below 40yrs	76% of the young: Dukes C&D	48% tumours are poorly differentiated or mucinous in young.
Australia	10	Turkiewitz 1971-1999	61/2384 below 40 years	Distribution of stage not significantly different in younger and older group	35% tumours in the young are poorly differentiated

Table 2. Summary of references in the literature on stage and tumour characteristics from Europe (inclusive of UK & Turkey) and Australia

Two of the reports from Europe listed in Table 2 (Sr.No.2,7) are entirely on young patients. One of these (Sr No. 2) has the largest study group of young onset patients (~250), while the other reports have ~100-150 (Sr Nos. 5,6,8) or less ~50 (Sr No. 1,4,7,10) young patients. The report, Sr No. 3 is on a much smaller population of 11 patients. A significant frequency of more advanced (C+D) tumour in the young (50-60%) was reported in several studies (Sr No. 2,3,5-7). This frequency was larger (76%) in a study from Turkey (Sr No. 9). Comparative assessment showed a higher frequency of advanced stages in the young as compared to that in the older patients (Sr No. 3-6). Significant frequency (~ ≤50%) of high grade tumours were reported in the young in several publications (Sr Nos. 3,5,7,9,10). Higher frequency of high grade tumours in the young as compared to the older group were cited in several other papers (Sr No. 1,3,5,7). Three studies (Sr No. 1,8,10) however, reported no difference in disease stage and one report (Sr No. 8) found no difference in tumour grade, between the younger and older patient groups. A significant occurrence of premalignant conditions in the young was reported in only one paper (Sr No. 2).

Country	Sr No	Reference, Period of Study	Age profile	Disease Stage	Tumour Characteristics
ASIA Iran	1	Fazeli 1995-2001	403 patients in two age groups, <40yrs and >40yrs	Older group: 53.2% in stage II; younger group: 45% in stage III.	Poorly differentiated tumours found in larger proportion in younger patients (22% vs. 5.9%)
Singapore	2	Kam 1989-2001	39 patients <30yrs, mean age 25yrs	Advanced disease stage in 70% patients.	Mucinous histology: 18%; differentiation: moderate 61%, poor 36%
	3	Chew 1997-2005	523 Asian cohorts 19-50 years Of them <40 yrs:134; >40yrs:389	63% Advanced stage (III-IV) <40yr group: 89/134;66% >40yr group: 245/389;63%	Predominantly poorly differentiated: (30% in <40 years 12% in >40 years) mucinous, signet ring cell histological subtypes (16% vs. 9%).
Malaysia	4	Shahrudin 1990-94	21 patients <30yrs	Extensive disease	Mucinous histology
Israel	5	Shemesh-Bar, 1997-2007	406 patients, 203 in <50 years	More advanced stage III-IV at diagnosis (56 vs. 41%) higher rate of N-2 disease (29 vs. 16%)	No difference in other features
	6	Neufeld 1999-2005	<50 years 90; 190 >50 years	40% Advanced stage (III-IV) <40yrs:47/90;52% >40yrs:61/190;32%	Mucinous tumour in 11% in early onset group, 7% in late onset group

Country	Sr No	Reference, Period of Study	Age profile	Disease Stage	Tumour Characteristics
Taiwan	7	Chiang 7 year period	5436 patients 7% <40 years	Dukes' stage improves with age (A & B 31% < 30 years, 49% > 80 years)	Poorly differentiated tumours tended to decrease with age, 16.9% < 30 years. 6.2% > 80 years. Similar trend in Mucin producing characteristics (36% vs 7.5%)
India	8	Nath 2003-2007	287 patients 35.6% < 40 yrs	Advanced T stage (T 0-2: 18.9% T -3: 62.3% T-4: 19.7% vs. 34.5%, 56.0%, 9.5%) and N-stage (N 0: 31.1%, N1: 41%, N2: 27.8% vs. 53.9%, 26.7%, 17.2%)	Poorly differentiated and / or mucinous or signet cell carcinoma (52% vs. 20.5%)
	9	Gupta 2000-2008	305 patients 40% < 40 yrs	60% presented in Dukes' stage III & IV	Mucinous tumour 80% Poor differentiation 50%
Nepal	10	Singh 2002 ^a	91 patients 28.6% < 40 yrs	92.3% present in Dukes' stage III-IV vs. 61.5% in older patients	Significantly higher poorly differentiated and mucinous carcinoma in the young.
SriLanka	11	de Silva 15 yr period	305 patients 19.7% < 40 yrs	No significant difference in Dukes' stage with older group	Significant presence of mucinous (13.3%) or signet ring type (5%) tumours.

Country	Sr No	Reference, Period of Study	Age profile	Disease Stage	Tumour Characteristics
AFRICA Egypt	12	Soliman* 1982-1996	1608 patients; 35. 6% <40 yrs	Dukes' stage is worse in > 40 years group (72% vs. 57%)	Tumour grade comparable in two groups; mucin producing tumours: 31% in younger group, 14% in older group

*Soliman et. al. (1997)

Table 3. Summary of references in the literature on stage and tumour characteristics from Asia and Africa.

Reports from Asia and Africa are listed in Table 3. Features of only the younger patients were assessed in four reports (Sr. No. 2-4,9). The younger groups were larger in several studies (523:Sr No. 3; 203:Sr No 5; 370: Sr No. 7 and 576 : Sr No. 12) from Asia and Africa as compared to ones from the USA (Table 1) and Europe (Table 2). Higher incidence of CRC in the young in Asia and Africa was found to be consistent with these figures. In two studies (Sr No. 11,12) the disease in the young was assessed as less advanced at presentation and less aggressive. In one report (Sr No. 5), a more advanced disease stage was noted but no difference in tumour grade was found. A more advanced disease and tumour grade was reported in the young as compared to the older patients (which is usually the case in Table 1 & 2) in 5 of 12 reports (Sr No. 1,6-8,10). In a report by Chew et. al (2009, Sr No. 3) the same conclusion was reached; 'older' patients were however in the age group 40-50 years. The frequency of advanced disease and high tumour grade in the young in these reports were similar to that in reports restricted to only the young patients (Sr No. 2,4,9).

Irrespective of the country, the size of the study group, time span and the year of study, the dominant result is the same. Young CRC patients present at a more advanced clinical stage, the tumours are mucinous and poorly differentiated, more so in comparison with the older patient group. The features in India and neighbouring Nepal and Sri Lanka are the same as in the rest of the world. We have noticed some difference in disease pattern in Asia and Africa as compared to the West in our discussions of the data in Tables 1-3. The issue of ethnic differences in determining the difference in disease characteristics is important. This issue, without specific reference to the disease in the young, received attention in several papers, e. g., Isbister (1992; New Zealand and Saudi Arabia), Soliman et. al. (2001; Egypt and the West), Fireman et. al. (2001; Arab and Jewish neighbours in Israel), Qing et. al. (2003; USA and China), Sung et. al. (2005; Asia and the West), Goh et. al. (2005; Asian patients of different races in Malaysia) and Fairley et. al. (2006; Blacks, Asians/Pacific Islanders and Whites).

The advanced stage at presentation of many colorectal cancers in young patients is not just a result of a delay in diagnosis. It may also be that the cancer in younger patients is more virulent by nature. This feature is rooted in subtleties of genetic differences. More aggressive' tumour characteristics, as evidenced by its mucinous nature and poor

differentiation have also been linked to molecular genetic differences. Recent molecular biology studies have shown characteristic features of mucinous carcinoma, e. g., lower expression of p53, more frequent DNA replication errors expressed as microsatellite instability and specific codon 12 K-ras mutations and, when ploidy has been determined, a higher index if diploidy was found than for non-mucinous carcinoma (Negri 2005).

Tumour subsite: The issue of subsite location is important in screening strategies and in choice of treatment protocols. In the literature (e. g. , Breivik et. al. 1997) preference for subsite location has been associated with molecular genetic roots of CRC. Molecular genetic findings classify CRC into two groups. The first class of tumours show microsatellite instability (MSI), occur more frequently in the right colon, have diploid DNA, behave indolently, of which Hereditary Non polyposis Colorectal Cancer Syndrome (HNPCC) is an example. The larger incidence of proximal colon cancer in patients with HNPCC syndrome highlights the importance of genetics in preference for subsite location in colon cancer. In the other group belong tumours which tend to be left sided, show aneuploid DNA, behave aggressively, of which Familial Adenomatous Polyposis (FAP) is an example. Each group has its own characteristic gene mutations (Lynch and de la Chapelle, 1999).

Breivik et. al. (1997) in a study of 282 patients from 7 hospitals in Norway in the period 1987-9 concluded that proximal and distal CRC evolve by different genetic pathways and that these pathways are influenced by sex-related factors. Their results, analyzed by statistical models, pointed to hormonal mechanisms with important clinical implications. They found that presence of TP 53 mutations was dependent on tumour location only, with a positive association to cancers occurring distally ($p=0.002$). Microsatellite instability was found almost exclusively in proximal colon cancers.

Stigliano et. al. (2008) compared a cohort of 40 HNPCC cases with 573 sporadic CRC cases in the period 1970-1993. Median age of diagnosis was 46.8 years in HNPCC cases and 61 years in sporadic CRC cases. 85% had right sided lesion in HNPCC group as opposed to 57% in sporadic cancer group.

Slattery et. al. (1996) studied age, sex and tumour sub-site distribution in 1709 CRC patients from three geographic areas in the USA. Approximately 50% of CRC in men and greater than 50% of CRC in women were in the proximal segment of the colon. Men who were diagnosed prior to age 50 and both men and women diagnosed at age 70 or older had predominantly proximal cancers. People with proximal cancers and those diagnosed prior to age 50 were likely to have more advanced disease. In general, both men and women had more proximal cancers with advancing age, which were associated with more advanced disease.

Ionov et. al. (1993) showed that 12% of CRC patients carried ubiquitous somatic deletions in poly (dA. dT) sequences and other simple repeats. Tumours with these mutations showed distinctive genotypic and phenotypic features. Patients with these deletions showed a predominance of right sided tumours while those without deletions had a predominance of left sided lesions.

Thibodeau et. al. (1993) studied the association of microsatellite alterations with preference for tumour subsite. All four sites of alteration studied showed a dramatic change in preference from distal to proximal colon in the mutated form (typical values: proximal/distal; (26,49), (11,1 in the mutated form)).

Fancher et. al. (2011) studied 45 young patients, 20 males and 25 females, mean age 43.6 years, in the USA and found preference for left sided lesions in females (16/8) and a preference for right sided lesions (12/10) in men ($p=0.35$; small sample size); right sided cancers had a higher stage at presentation.

Kaw et. al. (2002) studied 1277 Filipino patients of whom 218 (17%) were <40 years, a mean age of 31.3 years. Cancers of the right colon were noted to be more common in females (55%) and rectal tumours were seen more frequently in males (55%; $p=0.014$), but when analysed in relation to age, right colon cancers were actually more common in men <40 years of age ($p=0.013$); the incidence in women was higher only above the age of 50 years. The proportion of CRCs located on the right side was 28% for <40 years patients and 20% for the 40+ group. On the other hand, left colon cancers were seen in 30% of the older age group compared with 18% in the younger population ($p=0.001$). For rectal cancer, there was no significant difference in proportion between the young and the old ($p=0.414$).

Elsaleh et. al. (2000) in an older patient group (mean age 66.7 ± 12.9 years) in Australia reported that MSI positive tumours were slightly more frequent in women than in men (10 vs 7%). Right sided tumours were more frequently MSI positive than left sided tumours (20 vs 1%). Men with right sided tumours benefited from chemotherapy (37 vs 12%) but men with left sided tumours did not.

Mahdavinia et. al. (2005), Fazeli et. al. (2007) and Malekzadeh et. al. (2009) found that in Iranian patients with positive family history of CRC, the most frequently affected site of colon was the right side. Malekzadeh et. al. (2009) found that MSI was more frequent in early-onset patients and in proximal tumours. They reported that proximal and distal tumours harbor different p53 mutational spectra; distal CRCs showed a higher frequency of G to A transitions at CpG whereas G to A transitions at non-CpGs were more frequent in proximal tumours. Fazeli et. al. (2007) found that 62.5% of patients with proximal colon tumours were males.

Nelson et. al. (1997) and Saltzstein et. al. (1997) showed that there was an increase in the relative proportion of proximal colon cancers with increasing age 'a shift to the right'. Thus with increasing age, full length colonoscopy will be a better screening tool. The exact age at which the shift occurs will vary with gender and ethnicity. There is a predominance of African-Americans amongst those at risk for proximal colon carcinoma and predominance of white males amongst those at risk for distal CRC.

Goh et. al. (2005) in a study of different races in Malaysia observed that demographic differences between Asia and the West may exist. No difference in anatomic distribution was found in Malay, Chinese and Indian races. They noted that in general CRC tends to be located distally in areas with a lower incidence of disease (parts of Asia) and migrated proximally with increasing incidence, as in Japan or Korea. They suggested that this may be related to a decrease in rectal cancer and an increasing proportion of elderly patients in the population. Young patients had a higher probability of having distal lesions as compared to the older patients.

Qing et. al. (2003) in a comparative study on Chinese and American patients, noted that the proportion of left sided lesions in Oriental patients (74%) was significantly higher than that in Whites (63.7%) and that rectal cancers were significantly more common among Orientals ($p<0.001$).

O'Connell et. al. (2004^a) in their review quoted average values of subsite location in <40 years young patients as follows: ascending 22%, transverse 11%, descending colon 13%, rectum and sigmoid (including rectosigmoid junction) 54%, a dominance of left sided tumour in the young.

We summarize reports on preference for tumour sub-site from different countries in Table 4. Some of these are cited in Table 1-3 where patient groups are detailed. The others are detailed in Table 4.

	Sr. No.	Author, Country	Sub-site
Asia & Africa	1	Gupta, India	69.7% distal tumours in < 40 yr group (rectal 57.9%, left colon 11.8%). Of patients with colon cancer proximal tumours constitute 72%.
	2	Singh, South Asia*	Rectum: commonest (83%) site of the lesion in young patients (21-30 yrs). No comparison with older patient group.
	3	Singh, Nepal	Rectum: most frequent site of tumor (76.9% vs. 36.9% in older age group)
	4	de Silva, Sri Lanka	No significant difference in tumour distribution between the young and the old.
	5	Shahrudin, Malaysia	Rectosigmoid region: most common (29%) Left colon 19%, Splenic flexure 4%, Transverse colon 9%, Hepatic flexure 4%, Cecum 24% ;all patients <30yrs
	6	Goh, Asian patients of different races in Malaysia	No significant difference between < and > 65 years group; predominance (~90%) of left sided lesion in both age groups.
	7	Kam, Singapore	46% rectal and rectosigmoid; right-sided tumour: 20%; patient group, all young <30yrs
	8	Ashenafi, Ethiopia	66.7% rectal lesions; younger patients; mean age 47 years (61.4% <50 years, 36% <40 yrs, 16% <30 yrs)
	9	Shemesh-Bar, Israel	Higher proportion of left side tumour in the young (82% vs. 71%)
	10	Chew, Singapore (Asian patients)	Predominantly left sided tumour (~80%) in <40 years and 41-50 years age group; no effect of age.
	11	Malekzadeh, Iran	Predominantly right sided tumour, general population
	12	Ibrahim, Lebanon	Rectosigmoid most common site in general population (553 patients), 70.7%; also in 32, <29 years younger group: 84.4%
	13	Fazeli, Iran	Subsite distribution nearly independent of age group (< & > 40 years), distal ~ 80% in both groups.
	14	Chiang, Taiwan	No change in subsite preference from < 30 years to > 80 years
	15	Soliman**, Egypt	No change in subsite preference in < 40 years vs. > 40 years group, larger proportion of distal tumours (~65%) in both age groups

	Sr. No.	Author, Country	Sub-site
U. S. A.	16	Bedekian, USA	Increase in primary lesions in the right colon with increasing age at diagnosis; <40 yrs group compared with general population.
	17	Cozart, USA	Dominance of left sided lesions (12 right colon, 24 left colon, 11 rectum) and left colon amongst colon cancer patients; study group comprises of only young patients <30 yrs. No comparison with older group.
	18	Nelson, USA & Saltzstein, USA	Significant shift to right sided lesion with increasing age; <50 vs. >50 yrs.
	19	Slattery, USA	Proximal cancers more frequent (>50%) in men <50 years and in both men and women >70 years (details in text).
	20	Fairley, USA	Rectal cancers more frequent in <50 yrs group (37% vs. 26%); proximal colon cancer more frequent in >50 age group (42.6% vs. 32.1%), remaining <50% in both groups.
	21	Lichtman, USA	Older patients: more transverse/right sided lesions (p=0.003). 138 patients; mean age of patients with different sites of tumour: Right colon 72 yrs, left colon 66.1 yrs, rectum 61.6 yrs
	22	Karsten, USA	Right sided lesion more frequent (44%) in young compared to 21% in older group, p=0.004.
	23	Minardi, USA	Tumours evenly distributed in colon and rectum (under-40 group). Older group not compared.
	24	O'Connell ^a (International Review)	Rectum and sigmoid colon most frequent sites (54%) in the young <40 yrs patient group.
	25	Dozois, USA	Predominantly rectum (49.1%) or left colon (29.1%) than proximal colon (21.9%). All young patients <50 yrs. No comparison with older patient group.
	26	Behbehani, USA	Colon: Right 21%, Transverse 21%, Left 14% Sigmoid & Rectum 44% in the <40 yrs group; these figures are 34%, 4%, 8%, 54% respectively in the older group.
Europe	27	Leff, UK	Only 12% right-sided colon cancer, <40 yrs patients, no comparison with older group.
	28	Fante, Italy	Majority of tumours in left colon and rectum in the whole patient group <40 – 55 years. Right colon: 37% in <40 years, 18% in 41-50 years, 14% in 51-55 years group.

*Singh et. al. 1984; **Soliman et. al. (1997)

Table 4. Tumour Sub-site in the young in different countries

In some of these papers, (Sr. No. 1, 2, 5, 7, 8, 10, 17, 23-25, 27), a preference for distal lesions in the young patients were cited, but were not compared with the older patient groups. In some others (Sr. No. 3, 9, 12, 16, 18-21) this comparison was made and a change in preference for tumour sub-site with increasing age was noticed. Shemesh-Bar et.al. (2010, Sr. No. 9) and Ibrahim et. al. (1986, Sr. No. 12) found that although left sided lesions formed the majority of tumours, their proportion decreased in the older group. Singh et. al (2002^a, Sr. No. 3) and Fairley et. al. (2006, Sr. No. 20) found that the proportion of rectal cancers decreased with increasing age. In several reports preference for right sided lesions showed an increase with increasing age (Sr. No. 16, 18, 20-21). Slattery et. al. (1996, Sr. No. 19) reported an increase in proportion of proximal tumours with increasing age for women, exceeding 50% (62.3%), only in the age group 70-79 years. Amongst men, proportion of proximal tumours exceeded 50% in the <50 yr groups (62.5%, 30-39 yrs; 51.1%, 40-49 yrs), falls below 50% in the 50-59 and 60-69 yrs groups and then rises again to 54% in the 70-79 yrs group. A decrease in proximal tumours with increasing age was reported by Karsten et. al. (2008, Sr. No. 22) and Fante et. al. (1997, Sr. No. 28). Both studies reported a dominance of distal tumours in different age groups (two in Sr. No. 22, three in Sr. No. 28), but proximal tumours decreased with increasing age. In a few papers (Sr. No 4, 6, 10, 13-15, 26) sub-site preference was found not to depend on age. Fazeli et.al. (2007, Sr. No. 13) reported that ~80% of the tumours were distal in the young (<40 years) and also in the older age group. In these reports which did not find any effect of age on subsite preference, distal tumours were >50% in the young and in the older group. A preference for proximal tumours in a population of colon cancer patients were reported in several papers (Sr. No. 11 and Mahdavinia et. al. (2005) in general population of colon cancer patients from Iran, where incidence is lower than in the West and in Sr. No. 1 in young colon cancer patients < 40 years in India). Cozart et. al. (1993, Sr. No. 17) found tumour sub-site preference for left colon (24/12) in a small population of colon cancer patients; Dozois et. al. (2005, Sr. No 25) found the same preference in a much larger (1025 patients) young (<50yrs) population. We cite several prospective reports on change in relative preference of tumour sub-site over a long time period. Fazeli et. al. (2007, Sr. No. 13) reported that the nearly equal preference for distal tumours (~80%) in the <40 years and in the >40 years group in Iran, remained unchanged for two decades (1970-80, 1990-2000). In contrast, it was reported in a study on patients from New Zealand, in the period 1974-83 (Jass 1991), that the incidence of right colon cancers remained stable in younger patients (<50 years), that in older patients showed an increase and a marked reduction in left colon and rectal colon cancer in <50 years group was observed. An increase in proximal CRC relative to distal tumours was reported in another retrospective study in the period 1940-79 in the US (Beart et. al. 1983).

4. de novo CRC in Asia

The problem arising from inability to detect cancer early because of hospital infrastructure and relative lack of awareness of the disease may not be the only problem peculiar to the developing world in Asia and Africa. Sung et. al. (2005) pointed out that non-polypoidal (flat or depressed) lesions and colorectal neoplasm arising without preceding adenoma (de novo cancer) seemed to be more common in Asian than in other populations. Although most cases of colorectal cancer are thought to arise from a sequence of adenoma to carcinoma, evidence from Asia, in particular Japan suggests another mechanism. Clinicopathological studies have shown that there are two groups of colorectal cancer,

polypoid and non-polypoid (superficial) tumours. The latter are flat lesions with a raised or depressed surface. Since these tumours are small (<1cm in diameter) and there are no adenomatous elements in their vicinity, they were proposed not to have originated from any precursor lesion and were termed de-novo carcinomas. These non-polypoid tumours are less likely to have K-ras mutations than are CRC arising from the adenoma-carcinoma sequence. Non-polypoid tumours of the colorectal regions tend to reach deeper layers of the intestinal wall in the early stage of the disease and with a higher degree of dysplasia. They are therefore more invasive than the polypoid adenomas (Sung et. al., 2005). Reports on de novo cancer have been published from Japan (Goto et. al 2004) and from Taiwan (Chen et. al 2003). About one-third of CRC patients in both countries have de-novo cancer. One study from UK also reported this feature (Rembacken et. al., 2000). Whether this feature is unique to Asia or whether it shows any preference for the younger or the older group of patients is not reported. Because of their flat appearance they are harder to identify by conventional colonoscopy. Chromoendoscopy and the use of magnifying colonoscopy may be necessary. The absence of polypoid growth preceding malignancy has posed difficulties in screening for early CRC by radiological imaging or even endoscopic techniques.

5. Early onset CRC and genetics

Colorectal tumours provide an excellent model system for understanding the molecular events that control the process of initiation and progression of human tumours. Rate of random mutational events alone cannot account for the number of genetic alterations found in most human cancers and it has been suggested that destabilization of the genome may be a prerequisite early in carcinogenesis. In CRC there are two separate destabilizing pathways. The more common involves chromosomal instability (CNI). The second mutational pathway in CRC displays increased rate of intragenic mutation characterized by generalized instability in microsatellites (MSI). Defects in mismatch repair genes (MMR) lead to high frequency MSI in CRC. National Cancer Institute definitions of MSI-L (L=low), MSI-H (H=high) and MSS (microsatellite stable) in CRC are given in Boland et. al. (1998). A recently recognized molecular alteration found frequently in MSI cancers is the CpG island methylator phenotype (CIMP). Colon cancer is usually observed in one of three specific patterns: sporadic, inherited or familial. Fewer than 10% of patients have an inherited predisposition to colon cancer. Sporadic cancer is common in persons older than 50 years of age, probably as a result of dietary and environmental factors as well as normal aging. Patients with inherited disease have CRC at a younger age, 10-20 years earlier than general population and are of interest in this essay. The area of hereditary CRC has been reviewed by Lynch and de la Chapelle (2003) and earlier by Lynch et. al (1991). Different aspects of molecular genetics of CRC have been discussed in this series (Ewart Toland, 2012) and elsewhere (Fearon and Volgenstein 1990; Loeb 1994; Jass 1995; Lynch 1996; Baba 1997; Gryfe et. al. 1997; Lengauer et. al. 1998; Lynch and Smyrk 1998; Lynch and de la Chapelle 1999; Yang 1999; Potter 1999; Jass et. al. 2002; Calvert and Frucht 2002; Zbuk 2009). In this section we discuss several recent papers which highlight the difference in genetic characteristics of younger CRC patients and those of the older group.

Morris et. al. (2007) showed that the incidence of tumours with microsatellite instability was significantly higher in patients aged ≤ 40 years, 18.3% compared to 6.6% in those aged 41 - 60 yrs ($p < 0.0001$). TP53 mutations were also more frequent ($p = 0.002$). However K-ras mutations were less common ($p = 0.0001$) when comparing the same age groups. They

concluded that major age related differences in the clinical and molecular features of CRC exist.

Farrington et. al. (1998) pointed out that germ-line mutations in DNA mismatch-repair (MMR) genes impart a markedly elevated cancer risk, often presenting as autosomal dominant HNPCC. Not all gene carriers have a family history. Young probands with early onset CRC irrespective of family history were genetically tested and it was found that an appreciable proportion of young colon cancer probands carry a germline mutation in a DNA MMR gene.

Losi et. al. (2005) evaluated clinical features and molecular pathways, chromosomal instability (CNI) and MSI in early onset CRC. Of 71 patients (<45 years), 14 showed both MSI and altered expressions of MMR proteins. In the 57 MSI -negative (-) lesions, altered expression of APC, β -catenin and p53 genes were found more frequently than in MSI-positive (+) tumours. 7/14 MSI (+) tumours were associated with clinical features of HNPCC and in all but one, constitutional mutations in MLH-1 and MSH-2 genes could be detected. The same mutations were found in other family members. Involvement of chromosomal instability was demonstrated in a majority of early onset CRC.

Chan et. al. (1999) studied 59 Chinese patients <45 yrs and 58, >45 yrs in Hong Kong. The incidence of MSI-H varied statistically significantly with age, being observed in >60% of those <31 years at diagnosis and in <15% of those \geq 46 years. More than 80% of Chinese CRC patients <31 years had germline mutations in MMR genes. In a novel case, mutation in hMSH-6 was present but MSI was absent.

Ho et. al. (2000) in a study on 124 young (<50yrs) Hong Kong Chinese CRC patients concluded that MSI occurs in a significant proportion of the subjects. Young age at CRC diagnosis, proximal tumour location, increasing number of first degree relatives with CRC and a personal history of metachronous cancer were independent predictors of MSI status in the patient group. In patients <30 years, MSI tumours were more likely to be located in distal large bowel. In a proportion of patients with MSI tumours, germline mutation in the two MMR genes hMSH2 and hMLH1 was identified. The authors opined that this observation suggests a differential activity of the MMR pathway in colorectal carcinogenesis in different age groups. They observed that the inconsistency between MSI-H and a family history in the early onset patients deserves further attention.

Liang et. al. (2003) studied 138 below-40 CRC patients and 339 patients who were 60+. They found a higher percentage of normal p53 expression (61.1 vs. 46.8%, $p=0.023$) and high frequency microsatellite instability (MSI-H) (29.4 vs. 6.3% $p<0.001$) in the young. The family history of the two groups was similar.

Durno et. al. (2005, 2006) found evidence of MSI in 73% cancers from individuals in 9-24 years of age, 50% of whom had features of HNPCC. Other reports found MSI in 46% of under-21 patients with only 1/3 having a clear family history.

Sanchez et. al. (2009) performed a molecular classification of CRC based on microsatellite instability (MSI), CpG-island methylator phenotype (CIMP) and mutations in the K-ras and BRAF oncogenes. There were four classes, combinations of MSI-H and MSS with CIMP-H or CIMP (-). 69.8% of tumours (391 subjects) were MSS-CIMP(-) and less likely to be poorly differentiated ($p=0.009$). CIMP-H tumours were more common in older patients ($p<0.001$). MSI-H/CIMP-H tumours had a high frequency of BRAF mutation and a low rate of K-ras mutation, the opposite was true for MSS-CIMP(-) tumours ($p<0.001$). The four molecular phenotypes tended towards divergent survival. MSI-H cancers were associated with better disease free survival.

Alsop et. al. (2006) investigated association of young age in below-45 patients with somatic mutation of K-ras gene, a common event in CRC tumorigenesis. The role of these mutations was found to be comparatively minor in the younger group, in contrast to its significant role in CRC of older age of onset.

Soliman et. al. (2001) compared molecular pathology of CRC in Egyptian (44% <40 years) and Western patients. They found MSI-H carcinoma in 17% (2/12) of under-40 and 46% (12/26) of 40+ Egyptian patients; K-ras gene mutation in 0% (0/18) of under-40 group and in 17% (5/29) of 40+ group; p-53 overexpression in 57% (13/23) of under-40 group and 39% (13/33) of 40+ group. These data show that molecular pathology of CRC in young Egyptians differed from that in the old; in particular, K-ras mutation played a distinctly minor role in the younger group. Unique differences in molecular pathology of CRC between the Egyptian and Western patients were also discussed.

Breivik et. al. (1997) found that the presence of K-ras mutation was dependent on age and gender of the patient, with an especially low frequency amongst young males. Microsatellite instability was rare in tumours with K-ras and TP53 mutations.

Berg et. al. (2010) focused on the somatic tumour development in young patients with no known inherited syndromes. They studied mutations in oncogenes K-ras, BRAF, PIK3CA and the tumour suppressor gene PTEN and in TP53, in three age groups in 181 patients (45, < 50 yrs; 67, 51-70 yrs; 69, >70 yrs). Distinct genetic differences were found in tumours in the young and the elderly patients, who were comparable for known clinical and pathological variables. This result indicated that young patients had a different genetic risk profile for CRC development than older patients. Clinical implications of these differences were discussed by the authors. The total gene mutation index was lowest in tumours from the younger patients. In contrast the genome complexity assessed as copy number aberrations was highest in tumours from the youngest patients.

Casper et. al. (1994) showed in a study on 225 FAP patients that deletion of 5 base pairs at codon 1309 within exon 15 (the most common mutation) was identified in 20 families. Other mutations within exons 7-15 were found in 49 families. The 1309 mutation leads to development of colonic polyps at a younger age thus giving rise to an earlier malignant transformation. In patients with 5 base pair deletion at codon 1309, gastrointestinal symptoms and death from CRC occurred about 10 years earlier than in patients with other mutations.

Khan et. al. (2008) studied 35 patients with CRC diagnosed at <30 years age. They found no mutations in exons 4-10 of the p53 gene. The frequencies of polymorphism in p53 and in MDM2SNP309 did not differ from rates previously reported for normal control populations and no polymorphism in either gene could be associated with early onset CRC.

Ahmed et. al. (2005) reported a study on 363 CRC patients of whom 18 were of Bangladeshi origin. 22% of Bangladeshi patients presented with a locally advanced or a metastatic CRC, whereas the same figure for non-Bangladeshi patients was 11%. Sixty one percent of the Bangladeshi patients were below 40 years of age and did not report any family history. Microarray profiling between these two groups demonstrated 1203 differentially expressed genes ($p < 0.05$). The patient groups studied by Nath et. al. (2005) and by our group, (Gupta et. al. 2010) (Table 3) and by Pal (2006) belong predominantly to West Bengal in India, which is adjacent to Bangladesh. These studies reported dominance of younger patients in their study groups, advanced disease stage and aggressive tumour characteristics.

Liu et. al. (1995) studied the prevalence of DNA replication errors (RER) associated with genetic instability in relation to age among patients without HNPCC. RER was found in

cancers of several different types, particularly in HNPCC. CRC in majority of <35 years group (58% of 31 patients) exhibited instability whereas CRC in > 35 years group uncommonly did (12% of 158). In 12 of <35 years group, instability was evaluated for alterations of MMR genes and in 5, it was found to harbor germline mutations. These data suggested that the mechanisms underlying tumour development in young CRC patients differ from those in most older patients.

Lin et. al. (2010) showed in a study cohort of 950 patients (2000-2005) that carcinogenic effects of Western lifestyle might be mediated via insulin-like growth factor-1 (IGF-1). IGF-1 is a peptide growth factor that promotes cell proliferation and inhibits apoptosis. Both in vitro and in vivo studies suggested that IGF-1 could promote CRC growth. Further, circulating levels of IGF-1 were associated with various cancers including CRC. It was shown that genetic variation controls variability of circulating IGF-1. The expression of IGF-1 was reported to vary in different ethnicities. In turn it was speculated that polymorphisms of the genes involved in the IGF axis might affect IGF-1 expression and possible cancer risk. The age at onset of CRC varied considerably. Extreme age at the CRC onset, very young or very old seemed to be associated with different carcinogenesis. It was shown that some genetic polymorphism affects age of onset of cancers. For example IGF-1 polymorphism plays a significant role in affecting disease onset in Lynch syndrome. These authors showed that older patients have a higher frequency of AA genotype of IGF-1 (-2995C/A), significantly higher (12.7%) than that in younger patients (4.2%). Mucinous differentiation, but not other clinicopathological factors was associated with the CA/AA genotype of IGF-1. The authors concluded that the genotype of the IGF-1 promoter was different in young CRC patients compared to older CRC patients and that IGF-1 SNP was associated with mucinous adenocarcinoma.

Yantis et. al. (2009) provided data to show that post translational regulation of mRNA and subsequent protein expression may be particularly important to the development of CRC in young patients. They compared 24 patients <40 yrs of age with 45 patients \geq 40 yrs of age, who served as controls. Cases were evaluated for clinical risk factors of malignancy and pathologic feature predictive of outcome. More aggressive features in tumours of young patients, namely more frequent lymphovascular (81%) and venous (48%) invasion, an infiltrative growth pattern (81%) were reported. Significantly increased expression of miR-21, miR-20a, miR-145, miR-181b, and miR-203 was noted in the younger group.

6. Predisposing factors

Family history of CRC at a young age is a significant risk factor. Johns and Houlston (2001) performed a meta-analysis of 27 case-control and cohort studies of colorectal cancer risk and found that a family history of one affected first degree relative diagnosed before the age of 45 carried a 3.87 fold (95% confidence interval 2.40 - 6.22) increased risk for the disease. Fuchs et. al. (1994) concluded that a family history of CRC is associated with an increased risk of disease, especially amongst the young. The relative risk factor of an under-45 yrs person with one or more affected first degree relative as compared with those without a family history was 3. St. John et. al. (1993) performed a case-control study of relatives of CRC patients and of matched control patients. They concluded that first degree relatives of patients with CRC have an increased risk of colorectal cancer. The risk was greater if diagnosed at an early age and when other first degree relatives were affected. Winawer et. al. (1996) observed that siblings and parents of patients with adenomatous polyps were at

an increased risk for CRC particularly when adenoma was diagnosed at < 60 yrs age. Despite limited accuracy and compliance, family history is still the most easily obtainable risk factor for colorectal cancer.

Deficiency in host response to carcinogenesis is less easily recognized and treated. A personal history of other cancers, especially chronic immunosensitive cancers such as melanoma, if occurring at a young age, may indicate an increased susceptibility to CRC. Chronic immune suppression or clinical suggestions of impaired immunity may also mean the same.

FAP and HNPCC patients have a lifetime risk of 100 and 80 percent respectively, of developing CRC. In FAP, the affected persons develop hundreds to thousands of colonic polyps. Although the rate of transition to cancer is slow, the vast number of polyps virtually assures colon cancer development at a young age. Average age of developing cancer is 39 years, with 7% diagnosed by the age of 20 and 15% by 25. In HNPCC, the affected persons have a very high risk for CRC but do not develop the hundreds of polyps seen in FAP. These polyps are very likely to make a transition to cancer. Although sporadic colon cancer usually arises in colon polyps after a 5-10 years period of growth and transformation, in HNPCC this progression can occur within 1 -2 years. HNPCC occurs at a relatively young age, median 42-45 years, with 35%-40% diagnosed before 40 years of age. The proportion of HNPCC or familial colorectal cancer among all CRC varies by country from 1-10% with a median of 2-5% (Mecklin and Ponz de Leon 1994). HNPCC has been reported from many different populations, Europeans, white and Indian Americans, Asians, Australasians, South Americans and Egyptians (Sarrocá et. al. 1978; Bamezai et. al. 1984; Ushio 1985; Lynch et. al. 1985; Mecklin 1987; Vasen et. al. 1990; Mecklin and Jarvinen 1991; Jass and Stewart 1992; Soliman et. al. 1998).

Ulcerative colitis (UC) is another important predisposing factor. The most important risk factors for development of CRC in UC patients are prolonged duration of disease, pancolonic disease, continuously active disease and severity of inflammation. Eaden et. al. (2001) performed a meta-analysis of the risk of CRC in UC. 116 of 194 reported studies were included in this analysis. Overall prevalence of CRC in UC patients was 3.7%. The risk of CRC in UC patients was determined by decade of disease and a non significant increase in risk over time was observed.

7. Prognosis and survival of young patients

Opinion on the issue of survival of younger patients is not unanimous. We have divided literature reports on this issue, pre-2000 and post-2000, in two separate sections. The reports in which prognosis for the young is shown to be poorer and the ones in which they are not so, are separately grouped.

Pre-2000, poor prognosis: Moore et. al. (1984) concluded that poorer survival in younger (<40 years) patients was a result of an inherently more virulent lesion, a conclusion supported by a greater incidence of mucinous tumours, an indicator of poor prognosis and a higher incidence of advanced disease, especially in the second and third decades. They did not find delay in diagnosis as an important factor in determination of survival. Adkins et. al. (1987) ascribed poorer prognosis in the young (<35 years) to unfavourable histological features of the tumours and advanced disease at the time of presentation in these patients. Of 45 under-35 patients, 19 patients with poorly differentiated tumours survived for an average of 1 year, whereas 19 with well or moderately differentiated tumours survived for

an average of 4.5 years. Those few patients who presented early in the course of their disease responded well to radical resection. Okuno et al. (1987) reported frequent occurrence of mucinous carcinoma, lymph node involvement and advanced stage according to Dukes' classification in the younger group (<39 years). The overall survival rate was poorer in the younger group (41% vs. 55.9%), whereas the difference between the two groups in rates of curative resection was not statistically significant.

Pre-2000, favourable prognosis: Howard et al. (1975) found that younger patients had a greater frequency of advanced signs, later stages of cancer and mucoid carcinoma, but when compared by clinical stage, they did as well or better than older patients. 5-year survival rates were 31% in <40 years group and 32% in >40 years group. Clinical staging was the most important prognostic factor irrespective of age. No inherent difference was found in the virulence of cancer in the young, survival rate being essentially the same. Adloff et al. (1986) in a paper published much later reached identical conclusion. Walton et al. (1976) in a study on 70 under-40 patients reported that survival time was shorter in patients with mucinous and anaplastic tumours and their incidences increased in this age group. Overall survival rates, however, did not significantly depend on age. Early diagnosis and prompt aggressive surgical treatment produced survival equivalent to that in patients of other age groups. Scarpa et al. (1976) in a study on 47 adults in the age group 20-40 years found smaller tumours and depth of invasion as important prognostic factors but tumour grade had no correlation with survival. They concluded that there was no difference in survival rate between the young and the old. Bulow (1980) found, in an extensive study spread over 25 years (951 <40 patients, all <40 patients in Denmark in the period 1943-1967) that stage according to Dukes' classification and presence of intestinal obstruction and/or perforation and not age, determined prognosis. Ahlberg et al. (1980) in a study group of 27 patients, aged <30 years, in 1969-70 in Scandinavia, concluded that prognosis was good, if predisposing factors were absent (9/15 survived 5 years), but not so otherwise. Ohman (1982) in a study group of 1061 patients, of whom 48 were below 40, in Sweden reported a five year survival rate in the overall population and in curable cases. Both rates were equal in the two age groups. Age factor had no impact. Five year survival was 100% in stage A, 50% in B, 33% in C. Proportion of Dukes' A lesion was equal in the two groups; there were fewer B and more C lesions amongst the young. Survival was not altered if ulcerative colitis was superimposed on carcinoma. Beckman et al. (1984) studied 69 patients, 20-39 years and reported good prognosis. Neither age, sex, tumour size, location, mere presence of lymph node metastases, depth of tumour invasion nor predisposing disease of the colon was a strong prognostic factor. Metastases of six or more lymph nodes and distant spread of the tumour at the time of initial surgery were ominous findings; so was mucinous carcinoma, a relatively frequent occurrence. Jarvinen and Turunen (1984) in a study on 249 under-40 year patients between 1970 and 1979 found no difference in their 5 year survival rate from that of the general population. A premalignant condition was more common as age decreased. Family cancer syndrome, FAP and other predisposing diseases were observed in a significant proportion of study group. It was suggested that more emphasis should be placed on identification, family screening and treatment of conditions predisposing to colorectal cancer. LaQuaglia et al. (1992) analysed their experience with 29 histologically verified cases of whom 20 were resected for cure. The predictors for survival were resectability, regional nodal involvement, depth of invasion, grade (Signet ring (45%) or anaplastic lesions (24%) were considered high grade) and interval from symptom onset to diagnosis. Median age at diagnosis was 19 years (10-21 years), median survival was 16

months, that for those undergoing complete resection was 33 months. In those undergoing resection for cure, tumour grade, regional nodal involvement and depth of invasion were the only factors that affected prognosis. Hidalgo (1995) in Spain studied 26, under-45 CRC patients (17. 2% of the whole group) whose potential risk factors were no different from those of the general population. Clinical presentation, tumour site and Dukes' stage were similar in the younger group and in the general population, but morbidity, mortality and post operative complications were lower. There were no differences in resection or survival rates. Chung et.al. (1998) in a study on 101 under 40 patients and 2064 older patients found no difference in tumour characteristics, Dukes' stage and overall 5 year survival, but reported a higher adjusted hazard ratio and adverse outcome in the <40 years group compared to 40-59 years group. They noted that a significant family history and predisposing conditions in the young warrants aggressive screening, surveillance and treatment. Heys et. al. (1994) in a review reported histological evaluations of the cancers in the younger age group patients and found that approximately four times as many tumours were of the mucinous type. This was associated with an increased risk of local recurrence. Dukes' staging and vascular invasion by tumour were prognostic indicators for overall patient survival. However survival rates for young patients with CRC were comparable to those of older patients, when equivalent Dukes' stage was considered.

Post-2000, favourable prognosis: O'Connell et. al. (2004^b) used SEER (Surveillance, Epidemiology and End Results) database in the period 1991-1999 in the USA (1334 younger patients, 20-40 years; 46,457 older patients 60-80 years) to conclude that 5-year stage-specific survival was similar for stage I and III patients and better for younger patients in stage II and IV ($p < 0. 01$). The same patient group showed later stage (more of stage III and IV) and higher grade tumours for younger patients. The authors noted that their population-based finding contradicts earlier single institution reports. Stigliano et. al. (2008) compared a cohort of 40 HNPCC cases with 573 sporadic CRC cases in the period 1970-1993. Median age of diagnosis was 46. 8 years in HNPCC cases and 61 years in sporadic CRC cases. Early stage cancer (Dukes' A & B) was 70% in HNPCC group and 61. 6% in sporadic group. The crude 5-year cumulative survival for primary CRC was 94. 2% in HNPCC vs. 75. 3% in sporadic cancer patients ($p < 0. 0001$). The influence of age on prognosis is apparent.

Berg et. al. (2010) studied 181 patients (45, < 50 yr; 67 (51-70 yr); 69, > 70 yr) and found no difference in survival while comparing age groups, even when adjustment for tumour stage at diagnosis had been made. Younger patients however presented at a more advanced disease stage (54, 46, and 36% in three groups). Tumour stage was the most powerful prognostic variable ($p < 0. 001$). Turkiewicz et.al. (2001) in a study spanning 29 years in Australia concluded that young patients with CRC had the potential to do just as well. The overall 5-years survival among younger patients in Stage A and B (53%) was found to be better than their counterparts in the older group. With influence of a family history of CRC being very apparent in this group, the authors conclude that emphasis must be on screening. Makela et. al. (2002) in a study of 102 under-50 patients in Finland over a 20 years period (1980-1999) concluded that young age is not a poor prognostic marker in colorectal cancer. Radical operation, venous invasion and tumour grade were good predictors of survival in patients below 50 years. Kam et.al. (2004) in a study in Singapore on 39 under-30 years patients inferred that age did not affect survival and recommended early endoscopy for all with persistent symptoms. They concluded that early diagnosis, radical resection and adjuvant therapy still form the cornerstone in management of colorectal cancer in this age group. Karsten et.al.

(2008) in the USA performed a comparative study of two groups, < 40 years and > 60 years of age, ethnically diverse, between 1998 and 2005. Fifty one percent of 41 young patients were Hispanic. Young patients were more likely to have a family history. Aggressive nature of tumour in the young was noted, but operative intervention and survival was similar in the two groups. Tohme et. al. (2008) in a study of 325 patients, 13. 2% of whom were below 45 concluded that age by itself was not a significant prognostic factor. The independent prognostic factors were delay in consultation, which was more frequent in younger patients (29. 7 vs. 18. 6 weeks, $p=0. 01$), positive family history in the young (44. 1% vs. 18. 2%), right sided tumour and peritoneal carcinomatosis. Leff et. al. (2010) in a British study of 49, <40 patients reported a 5-year and overall survival of 58% and 46% respectively. They concluded that prognosis in the young was not worse than that for CRC in the population as a whole. Mitry et. al. (2001) reported, in both overall and stage for stage comparisons that patients below the age of 45 years had a better survival rate than older patients, mortality rate was lower in the younger group (2. 1% vs. 8. 4%) although advanced stage presentation was more frequent and predisposing conditions were significantly higher in the below 45 group (11. 7 vs. 0. 4%, $p<0. 001$). Lin et. al. (2005) studied 45 histologically confirmed under-40 patients, 90% of whom reported with advanced (C+D) stage, between 1992-2002 in Taiwan. They reported that disease stage was an important prognostic factor, 5 year survival in B, C and D stage patients being 25, 16, and 0% respectively. Karnofsky performance status ($KPS \geq 70\%$), lymph node involvement and preoperative LDH levels were major determinants of survival. Surgical resection and adjuvant chemotherapy improved survival of advanced stage patients, but the improvement achieved does not reach the level of a patient who reports early. Liang et. al. (2003) reported that although the younger patients with colorectal cancer had more mucin producing (14. 7 vs. 4. 7%, $p<0. 001$) tumours and a more advanced tumour stage at presentation ($p<0. 001$) than older patients, the operative mortality rate was lower (0. 7 vs. 5%) and cancer specific survival was similar ($p<0. 05$) in stage I, II, III disease or better in stage IV disease (22-28 vs. 12-17 months, $p<0. 001$).

Post-2000, poor prognosis: Endreseth et. al. (2006) in a study on 2283 rectal cancer patients found overall 5-year survival to be 54% for patients younger than 40 years compared to 71-88% for the older patients ($p=0. 029$). Among those treated for cure, 56% of <40 group developed distant metastasis compared to 20-26% in the older group. Age younger than 40 years was a significant prognostic factor in this group and increased the risk of metastasis and death. A study from Nepal by Singh et. al. (2002^a) reported a more aggressive disease in the younger group (<40 years) and a significantly lower 2 years survival rate (4% vs. 55%). Singh et. al. (2002^b) in a study on 18 under 40 patients in India found that the tumor was unresectable in 5 patients (28%). Fourteen patients (78%) had advanced cancer indicated by TNM stage III or IV disease. Among the 13 patients subjected to surgical treatment followed by adjuvant chemotherapy, only 3 had long term disease free survival beyond 2 years.

Prognosis and Genetics: There have been reports in the literature that suggest that the survival of MSI-H CRC patients is longer than that of patients with MSS CRC. This latter group constitutes the majority. In some studies however no survival advantage was detected and a National Cancer Institute workshop held in 1998 (Boland et. al. 1998) concluded that MSI had not been shown to be an independent predictor of prognosis (Gryfe et. al., 2000). We cite a number of mostly post-2000 papers that link prognosis to MSI tumour pathway.

Gryfe et. al. (2000), in a study on 607 under-50 patients found MSI in 17% of patients and concluded that MSI was associated with a significant survival advantage independent of all standard prognostic factors including tumour stage. Regardless of depth of tumour invasion, MSI-H CRC had a decreased likelihood of metastasis to regional lymph nodes. Elsaleh et. al. (2000) (mean age 66. 7±12. 9 years) in Australia report striking survival benefits for patients with MSI tumours (90 vs 35%, p=0. 0007) and also for patients with right sided lesions, who received adjuvant chemotherapy as compared to those who did not (48 vs 27% alive at end of study, p<0. 0001) and for women (53 vs 33%, p<0. 0001). Suh et. al. (2002) in a comparative study of MSI(+) and MSI(-) sporadic young (<40years) CRC patients showed that the former had better prognosis (p=0. 051). Their results suggested that sporadic MSI(+) CRC in the young had different histomorphologic features as compared to MSI(-) CRC and HNPCC cancers. Samowitz et. al. (2009) in a study of 990 rectal cancer patients in the US showed that even though MSI-H has been associated in many studies with improved prognosis of colon cancer, the effect of MSI-H and K-ras mutations posed significantly higher risk of death for rectal cancers. Liang et. al. (2003) reported that there was a higher percentage of normal p53 expression (61 vs. 48%) and high frequency microsatellite instability (MSI-H) (29. 4 vs. 6. 3%, p, 0. 001) in the young. Lukish et. al. (1998) in a study group of 36 patients in the <40 year age group determined their DNA replication error (RER) status (expressed as MSI) and compared the clinical and pathologic characteristics of RER(+) and RER(-) cases. They concluded that RER(+) tumours were common (47%) in young patients and patients with RER(+) tumours had a significantly improved prognosis: 5 year survival probability 68% in RER(+), 32% in RER (-) tumours (p<0. 05). Knowledge of RER status therefore could affect initial therapy, postoperative chemotherapy and follow up.

The paradoxical good survival after surgery for patients with young age at diagnosis of CRC supports the idea that many cancers in the young are microsatellite unstable. A number of studies linked high frequency MSI to poor tumour differentiation or mucinous histology, a signature of many tumours in the young (Sanchez et. al. 2009; Kim et. al. 1994, Lin et. al 2010, Suh et. al., 2002). Ionov et. al. (1993) in their study of mutations involving poly (dA. dT) sequences (Section 5 for details) found that the presence of mutations was accompanied by an increase in the proportion of poorly differentiated lesions (6/9 vs 17/90, poor/well, moderate) and also in an increase in proportion of Stage A +B disease (2/14 vs 53/68; C+D/A+B). Crude survival was expected to be better than usual in young patients because of their youth and the improved tolerance to surgery and complications that youth confers (Liang and Church 2010).

Berg et. al. (2010) in a study of patients in different age groups (Section 5 for details), found that patients with TP53 mutated tumours had poorer survival rates than patients with wild type TP53 (938 vs. 1016 days, p =0. 04); however the difference was not significant when corrected for tumour stage. TP53 mutation were of higher prognostic significance in right sided tumours (883, 1051 days; mutated, wild type; p = 0. 005). Among patients in the younger age group, those with K-ras mutation had significantly shorter survival than patients with K-ras wild type samples (841, 1033 days, p=0. 02).

Barnetson et. al. (2006) studied a group of 870 below-55 years CRC patients for germline mutations in DNA MMR genes, proposed a model for prediction of the presence of mutations in these genes and validated the model in an independent group of 155 patients. Survival in carriers and non carriers was similar.

8. Molecular genetics and treatment protocol

Chemotherapeutic treatment protocol will progressively become more specific as the genetic basis of CRC gets better understood and the heterogeneity of the disease is better characterized. There are several literature reports that show these connections.

Fallik et. al. (2003) studied response to irinotecan in 72 patients, of whom 1 responded completely and 11 partially. Among the 7 tumours that displayed MSI-H phenotype, 4 responded to irinotecan whereas only 7 out of 65 MSI-L tumours did ($p=0.009$). A better response to irinotecan was observed in the patients whose tumours have lost BAX expression ($p<0.001$). 7 of 72 tumours had inactivating mutations in the coding repeat of the target genes. Amongst these seven, five responded to irinotecan, whereas only 6 of the other 65 tumours did ($p<0.001$) indicating that MSI-driven inactivation of target genes modifies tumour sensitivity. It has been shown that tumours with mucinous histology, a common feature of many tumours in the young (section 7) and whose molecular genetic signatures have been referred to earlier (section 3), show poor response to fluorouracil-based first line chemotherapy (Negri et. al. 2005) and first-line oxaliplatin /irinotecan based combination chemotherapy (Catalano et. al. 2009).

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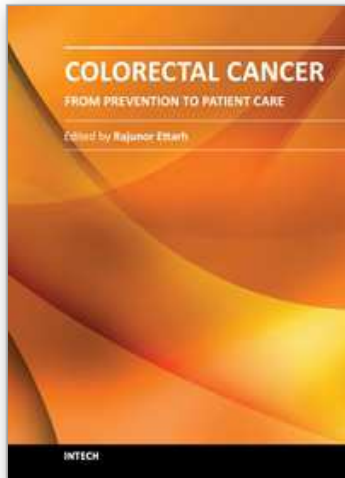
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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