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Original Article

Young onset colorectal cancer: How does it differ from its older counterpart?

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Abstract

BACKGROUND: Colorectal cancer in the young has been a debated topic in literature with conflicting reports as to its pattern of occurrence and survival as compared to the older age group. **MATERIALS AND METHODS:** Retrospective study to analyze the clinicopathological characteristics, treatment modalities and survival of sporadic young-onset colorectal cancer (YOCR) patients (<40 years) and compare them with the older group (>40 years). **RESULTS:** Of 172 patients managed, 72 (42%) were in the YOCR group. Among 72 patients, six were excluded because of hereditary syndromes. Incontinence ($P = 0.02$) and obstruction at time of presentation ($P = 0.03$) was significantly more common in the YOCR group. Left sided disease was more common in YOCR group (47/66) compared to the older group (65/100), but the difference was not statistical significant ($P = 0.45$). The proportion of rectal cancers was significantly more in the YOCR group (39/47) compared to the older group (39/65) ($P = 0.01$). Significant difference in resectability was noted in the left sided (YOCR 26/47 vs. older 49/65 $P = 0.04$) and the rectal cancers (YOCR 18/39 vs. Older 29/39 $P = 0.02$). The survival was similar among the two groups. **CONCLUSIONS:** Sporadic colorectal cancers in the young are more advanced and less resectable when compared to older population. Genetic studies are needed to elaborate the reasons for left sided predominance and aggressiveness of sporadic colorectal cancers in the younger subgroups.

Key Words: Anterior resection, colorectal cancer, young onset

Introduction

Colorectal cancer in the young is a much debated topic in literature with conflicting reports as to its pattern of occurrence and survival when compared to the older age group. There are reports that talk of these malignancies to be predominantly left sided and to be more advanced with a poorer prognosis.[1-5] Simultaneously, there are some reports that suggest young colorectal cancers of being predominantly right sided[6,7] and having a better stage-specific survival when compared to the older age group.[8,9] This is further complicated by the fact that most studies have not excluded patients with ulcerative colitis and hereditary cancer syndromes.[2,4,6,7] The reports of single center studies of the eighties and nineties varied with a wide range showing no consistent pattern. An early report in the eighties showed a similar distribution of the sites of colorectal cancer in the young and the old with a better survival for the young.[10] Minardi *et al*.[4] stated that colorectal cancer is distributed evenly throughout the colon in young patients though it is diagnosed at a more advanced stage when compared to the elderly. Fairley *et al*.[3] stated in 2006 that rectal cancers were diagnosed more commonly and proximal cancers less commonly in young patients <50 years compared to adults. O'Connell *et al*.[8] stated that the 5 year stage specific survival in stage two and four is actually better in the young onset colorectal cancer (YOCR) group when compared with the old. The population-based studies that came in 2000 had different results as far as survival was concerned and they did not place emphasis on the details of the modalities of treatment these patients received.[11-13] Most of the reports are from the west and there are no reports from the Indian subcontinent. Therefore, we took up this study to analyze the patterns of YOCR in the subset of Indian population that attended our tertiary center for the last 10 years and compared them with the older age group colorectal cancer patients who attended our hospital during the same time period.

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Materials and Methods

All colorectal cancer patients who attended the outpatient department of our surgical unit and received treatment either in the form of surgery, preoperative neoadjuvant therapy, adjuvant therapy or palliative chemotherapy in our hospital from 2003 to 2012 were analyzed retrospectively from a prospectively maintained database.

We divided patients into two groups (a) the YOCR group including patients with age up to 40 years (b) the older group (O), including patients with age more than 40 years. Patients with ulcerative colitis and known hereditary cancer syndromes were excluded from the study in order to estimate the true nature and trends of the sporadic colorectal cancer in the young.

The age wise subgroup analysis was done in young onset group by dividing the young group into up to 20, 21–30 and 31–40 subgroups. Stage-wise analysis was performed according to TNM classification AJCC seventh edition.[14]

Parameters analyzed

Location of the tumor, clinical presentation, histopathology, carcinoembryonic antigen (CEA) levels, stage distribution, resectability and survival were analyzed and compared between the two groups.

Work up and management policy

In our institution, complete work up of patients presenting with colorectal cancer include serum CEA levels, contrast enhanced computed tomography (CECT) scan of abdomen and pelvis and colonoscopy. Magnetic resonance imaging was done in selected patients with rectal cancer. Early stage disease was taken up directly for the operation, and laparoscopic approach was attempted on the discretion of the surgeon. Locally advanced mid and lower rectal disease (t3 and above/nodal disease) were planned for neoadjuvant chemoradiotherapy, followed by operation. This policy of neoadjuvant chemoradiotherapy was followed during the latter half of the period of this study while the patients in the initial half were subjected to the operation followed by adjuvant therapy. Patients with metastatic disease

presenting with obstruction underwent a decompression stoma followed by chemoradiotherapy and reassessment. Locally advanced colonic cancer including rectosigmoid tumors underwent resection followed by adjuvant therapy. Metastatic colonic cancer underwent palliative resection, bypass or stoma depending upon the extent of adjacent organ involvement and metastasis followed by chemotherapy.

Follow up

Our follow up strategy was to review patients postoperatively every 3 months with serial CEA and physical examination, CECT abdomen for patients at high risk of recurrence annually for 3 years, colonoscopy at 1 year that would be repeated at 3 years and then every 5 years.

Statistical analysis

All the data were enumerated using Microsoft excel 2007 by Microsoft Inc., and Fischer's exact test for categorical variables available at Graphpad Software quickcalcs by Graphpad software, Inc. was used for statistical analysis. Log rank test of SPSS 16 software by SPSS Inc was used to compare the survival curves of the young versus old in the various stage subgroups.

Results

A total of 172 patients of colorectal malignancy were managed from 2003 to 2011. There were 72 patients in the YOCR cancer group and 100 patients in the older group. Of 72 patients in YOCR group, six patients having predisposing conditions (ulcerative colitis $n = 2$, familial adenomatous polyposis $n = 1$, juvenile polyposis coli $n = 1$, Peutz jegher syndrome $n = 1$ and neuroendocrine histology $n = 1$) were excluded.

The incidence of YOCR cancer was 42% among colorectal cancer patients attending our outpatient department in this study. The male: Female ratio was 1.5:1 in the YOCR group while 4:1 in the older group with a statistically significant difference ($P = 0.01$).

Location of the tumor

The distribution of left and right sided cancers is listed in Table 1. In YOCR group 47 (71%) patients were left sided. In a subgroup analysis, eight patients were seen in up to 20 years. All had left sided rectal disease. Among 17 patients in age group 21–30 years, 13 (76%) had left sided rectal cancers. Patients between 30 and 40 years had both right sided (37%) and left sided tumors (63%). In the older group, 35 patients had right sided tumor while 65 were left sided cancers. Thus left sided disease was more common in the younger age group compared to the older group but the difference was not statistically significant ($P = 0.45$). The difference attained statistical significance among age <30 years ($P = 0.03$). In YOCR group among 47 left sided tumors, 39 patients had rectal or rectosigmoid tumors while in the older subgroup among 65 left sided tumors, 39 had rectal or rectosigmoid tumors. The difference was statistically significant ($P = 0.01$).

Clinical presentation

The median duration before presentation was similar among YOCR (6 months [range 1 month–4 years]) and older group (6 months [range 1 month–3 years)]. Various clinical symptoms included bleeding per rectum, altered bowel habits, anorexia, lump abdomen, obstruction, tenesmus, pain abdomen, incontinence, easy fatigability and incomplete defecation. A comparison of clinical features in the younger group to the older group is shown in Table 2. Incontinence ($P = 0.02$) and obstruction at time of presentation ($P = 0.03$) was significantly more common in the YOCR group.

Histopathology and carcinoembryonic antigen level

In the older group out of 100 patients, 15 had mucinous, and 14 had poorly differentiated tumor while in YOCR out of 66 patients, 15 had mucinous, and nine had poorly differentiated tumors. The difference was not significant ($P = 0.39$). The median CEA level in YOCR (6.06 ng/ml) was similar to that in the elder age group (4.75 ng/ml).

Stage distribution[Table 3]

In YOCR, 75% patients were either in stage three or stage four disease compared to 62% patients in the older group as shown in Table 3. Metastasis was detected in 20 out of the 66 in the young group, whereas in the older group 18 out of 100 patients had metastatic disease ($P = 0.08$). The

Table 1: Left and right sided colon cancers in the various subgroups

Subgroups (years)	Up to 20	21-30	31-40	Young (*n*=66)	Older (*n*=100)
Right side	-	4	15	19	35
Left side					
Splenic flexure, descending and sigmoid	-	-	8	8	26
Rectum/rectosigmoid	8	13	18	39	39

Table 2: Comparison of the symptoms of colorectal cancer in the young with that in the old

Symptom	Young *n*=66 (%)	Elder *n*=100 (%)	*P*
Bleeding per rectum	44 (67)	56 (56)	0.19
Altered bowel habits	35 (53)	65 (65)	0.14
Incomplete defecation	6 (9)	6 (6)	0.54
Incontinence	8 (12)	3 (3)	0.02
Easy fatigability	13 (20)	17 (17)	0.68
Pain abdomen	41 (62)	51 (51)	0.20
Weight loss	40 (61)	58 (58)	0.75
Anorexia	30 (45)	43 (43)	0.87
Lump	13 (20)	17 (17)	0.39
Obstruction	17 (26)	12 (12)	0.03
Tenesmus	12 (18)	11 (11)	0.25

Table 3: Stage-wise distribution of colorectal cancers among various subgroups

Stage	Up to 20 years	21–30 years	31–40 years	Young group *n* (%)	Older group *n* (%)
I			3	3 (5)	6 (6)
II	1		12	13 (20)	32 (32)
III	5	7	18	30 (45)	44 (44)
IV	2	10	8	20 (30)	18 (18)

site of metastatic disease in older group was peritoneal $n = 10$, liver $n = 6$, combined $n = 1$ and supraclavicular lymph node $n = 1$ and in YOCR was peritoneal $n = 13$, combined $n = 3$ liver $n = 2$ and lymph nodal $n = 2$.

Management

The surgical treatment received by these patients is listed in Table 4. In the YOCR group among 19 patients with right sided tumor 14 (82%) underwent resection while four had bypass, and one patient received palliative chemotherapy. Of 47 left sided tumors, only 26 (55%) underwent resection while 15 patients had laparotomy and colostomy/ileostomy, and five patients were managed without surgical intervention. In the older group among 35 patients with right sided tumors, 30 (86%) underwent resection, three patients had bypass and ileostomy was done in remaining two patients. Among 65 left sided tumors 49 (75%) underwent resection while three patients had bypass, seven had colostomy and remaining seven were not offered surgical treatment. The resectability rate was not statistically significant among the right sided cancers when compared between two groups (YOCR74%vs. Older 86% $P = 0.29$). While there was a significant difference in resectability rate among the left sided tumors between YOCR group (55%) versus older group (75%) ($P = 0.04$). In the subgroup analysis of left sided tumors, 29 out of 39 patients with rectal or rectosigmoid tumors were resectable in the older group compared to only 18 out of 39 patients in YOCR group ($P = 0.02$).

Among 18 patients in YOCR with locally advanced ($n = 6$) and metastatic ($n = 12$) disease who received anterior chemoradiotherapy only four patients underwent resection. There was a partial response in two patients and stable disease in other two.

Survival

The overall survival of patients in YOCR group was 38% while in the older group was 36% at 48 months ($P = 0.41$). In stage wise analysis, overall survival of patients in stage II was 60% in YOCR group and 70% in the older group at 36 months ($P = 0.33$). The overall survival of patients in stage III was 39% in YOCR group and 29% in the older group at 48 months ($P = 0.46$). None of the patients in stage IV survived at 24 months in YOCR group and at 18 months in older group = 0.14. The stage wise comparison of survival of YOCR with an older group is shown in Figure 1.

Discussion

In our experience increasing number of colorectal malignancies are being seen in the younger age group. There are variable reports in the literature as regards the incidence of colorectal cancer in the young. A population based study[8] concluded that it was 3%. However, reports from single center studies vary from 0.4% to 35%.[2,15,16] In our center this incidence was 41% even after taking 40 years as cut off. Although, there could be some referral bias of the tertiary center but this incidence is definitely high in the patients in the younger group.

The distribution of these tumors among females increases in the YOCR group. The male female ratio decreases from 4:1 in the older group to 1.5:1 in the younger group.

There are conflicting reports in the literature about the most common site of colorectal cancer in young adults. Some studies say that right sided are more common[6,7] where as others suggest that the left sided are more common.[2,8] However, in most studies the hereditary syndromes and ulcerative colitis related cancers were not excluded[2-4,6,7] therefore it does not reflect the true status of sporadic YOCR. It is important to exclude patients with predisposing

Table 4: Various surgical procedures performed in both groups

Site of tumour	Procedure	Young onset colorectal <40 years			Older group >40 years
		<20 (*n*=8)	20-30 (*n*=17)	30-40 (*n*=41)	*n*=100
Right side	Right hemicolectomy	-	3	11 (Lap 1)	27 (Lap 3)
	Subtotal colectomy	-	-	-	3
	Palliative ileotransverse bypass	-	1	3	3
	EL+ileostomy	-	-	-	2
	Palliative chemotherapy	-	-	1	-
Left side	Left hemicolectomy	-	-	5 (Lap 1)	9
	Low anterior resection	1	-	5 (Lap 1)	9 (Lap 1)
	Anterior resection	2	1	3	7 (Lap 1)
	Sigmoidectomy	-	-	1 (Lap)	9
	Abdomino-perineal resection	3 (Lap 1)	2	3 (Lap 2)	14 (Lap3)
	Subtotal colectomy	-	-	-	1
	EL+colocolic bypass	-	-	-	3
	EL+colostomy	1	7	5	6
	EL+ileostomy	-	1	1	-
	EL+assessment	-	-	1	-
	Palliative CTRT	1	2	2	7

EL=Exploratory laparotomy; Lap=laparoscopic; CTRT=Chemoradiotherapy

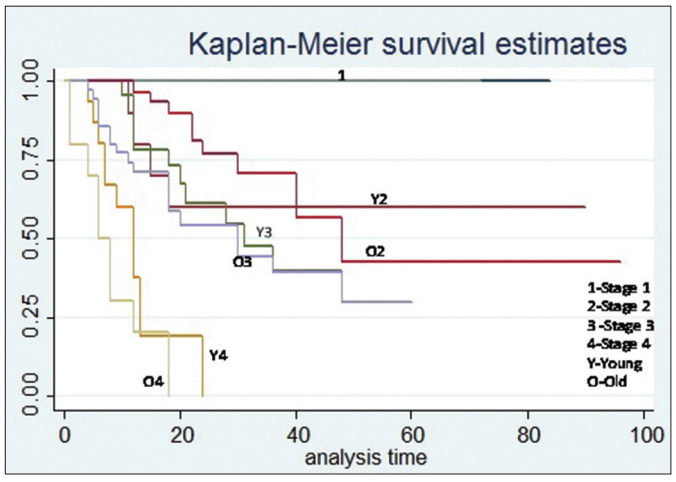

Figure 1: The stage-wise comparison of Kaplan–Meier survival curves of young onset colorectal cancer with the older group

conditions as screening in these patients can help in early detection that may change the outcome. We have excluded all hereditary syndromes and ulcerative colitis in order to address the true presentation of sporadic YOCR. We found YOCR patients to have a predilection to left sided tumors. Among left sided tumors, most of them were located in the rectum or rectosigmoid area. We also noticed that the younger the age group more was the incidence of left sided tumors. In 30–40 age group there were 15/41 right sided tumors, this reduced to 4/17 in the 20–30 age group which further reduced to 0/8 in up to 20 years.

According to O'Connell *et al*., an average of 22.7% of YOCR patients had family history of colorectal cancer.[2] Mahdavinia *et al*.[17] reported that the distribution of tumor site differed significantly between those with family history of colorectal cancer and those without this history. The authors evaluated 112 patients <45 years and found that individuals with a family history of colorectal cancer often had tumors localized to the proximal colon, but 77% of patients without a family history of colorectal cancer had tumors of the distal colorectum. In our study, we have found a similar left sided predominance (71%) in the younger age group. None of these patients had positive family history.

We found that the sporadic colorectal carcinomas of the younger age group were significantly more advanced at time of presentation. For young patients who develop colorectal cancer, but have no known predisposing genetic risk factors, late diagnosis and poor outcomes may result from the clinician's failure to consider the possibility of malignant disease in the differential diagnosis.[16] However, in our series the median duration of symptoms before presentation was similar among both groups that is, 6 months. This suggests aggressive nature of the disease in YOCR group thereby resulting in advanced disease at time of presentation. Presence of incontinence and obstruction at time of presentation was significantly more common in YOCR group. This again shows sporadic YOCR are more advanced with a left sided predilection. In Table 5 we have listed similar studies that have addressed sporadic young colorectal cancers and compared their attributes with ours. Minardi *et al*.[4] found that 42% of the YOCR patients had mucinous differentiation while this pattern was less prevalent in the older population. O'Connell *et al*. suggested that this higher prevalence of mucinous/poorer differentiation is associated with the poorer prognosis and 5 year survival found in the younger group.[2] However, hereditary syndromes were not excluded in the studies analyzed. Mucinous differentiation being a marker for microsatellite instability is found in hereditary colorectal cancer. Yantiss *et al*.[18] reported a minority (13%) of patients with mucinous differentiation and attributed it to the fact that 92% of their patients did not have any genetic risk factors. They suggested that the inclusion of proximally located colonic cancers with underlying known genetic predisposition in such studies account for the reportedly high incidence of mucinous/poorer differentiation. Our results agree with this since there is no statistically significant difference in the incidence of mucinous/poorer differentiation in YOCR (36%) when compared to the older group (29%) having excluded all patients with family history of colorectal cancer.

Tumors in sporadic YOCR were less resectable compared to those in the older age group. This difference was significant for the left sided tumors (YOCR 26/47 vs. older 49/65 $P = 0.04$). Among right sided tumors, the resectability rate was not statistically different among YOCR (74%) and older patients (84%) $P = 0.29$. The incidence of metastatic disease was higher in YOCR group compared to the older ($P = 0.08$) group. In literature, few studies that have excluded hereditary syndromes have not analyzed and compared the resectability rates of the young colon cancers with the old.[16] Among the other studies, the resectability rate for the young colon cancers ranged from 68% to 93%.[2,5,9,10]

In our study, there was no significant difference in the survival of young versus old patients. O'Connell *et al*. reported that the stage specific 5 year survival for young in Duke's A and B is better than the old in a literature review but a population based study found that the stage specific survival was better in the young in stage 1 and 4.[2,8] Petrek *et al*. and Turkiewicz *et al*. have reported better overall survival in the young patients compared to the old.[9,10] Minardi and Domergue, on the other hand, reported poorer overall 5 year survival especially in stage C and D young patients.[4,5] It is important to note many of these studies have not excluded hereditary colorectal syndromes.

In large scale population based studies based on cancer registries, they have stated that the results have potential limitations and no information on any adjuvant therapy such as chemotherapy were available.[8] In this study we attempted to overcome these limitations of previous studies. We studied the clinical, histological characteristics of YOCR with emphasis on the treatment they received, outcome and survival and then compared them with the older colorectal cancer patients.

One of the limitations of our study is that in this retrospective analysis we have excluded hereditary syndromes only by a detailed family history of the patient and not by genetic markers. There have been reports of a category of Microsatellite stable tumors among the sporadic early onset

Table 5: Comparison of studies including sporadic young onset colorectal cancer

Authors	Age criteria (years)	*n*	Region	Site	Significant feature	Resection rate %	Mucinous %	Met %	5 year survival
Minardi *et al*.[4] 1998	40	37	US	R=L	42% recurrence rate	70	42	22	Poorer compared to older
Dozois *et al*.[16] 2008	50	1025	US	L>R	Largest cohort	NA	11	34	NA
Present study	40	66	India	L>R	Poor response to CTRT	61	22	30	Similar to older

R=Right; L=Left; CTRT=Chemoradiotherapy; Met=Metastasis; NA=Not available

colorectal cancers where in the tumors are predominantly left sided and associated with fairly advanced disease.[7,17] Hawkins *et al*. stated that diploid microsatellite stable tumors represent an aggressive subset of sporadic colorectal carcinomas.[19] Mourra *et al*. suggested that the tumor suppressor gene located in chromosome 14 might have a role in microsatellite stable colon carcinogenesis and that it seems to be more frequently involved in early onset cases.[20] However, Boardman *et al*. concluded in their study that first degree relatives of microsatellite stable colorectal cancer patients do have an increased risk for the development of GI tract cancer in general and of colorectal cancer in particular and that this variety may confer an increased familial risk for CRC that follows an autosomal recessive pattern of inheritance.[21] It would be interesting to see if the left sided cases in the younger subgroups are linked to an unknown genetic etiology such as the microsatellite stable variety reported in the literature.

Conclusions

Thus, our study indicates that the sporadic colorectal cancers of the young are predominantly left sided. They are more advanced and less resectable when compared to the elderly population. Genetic studies are needed to elaborate the reasons for left sided predominance and aggressiveness of these sporadic colorectal cancers in the younger subgroups.

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