

Diagnosis of Colon Cancer Differs in Younger versus Older Patients despite Similar Complaints

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ABSTRACT: **Background:** Colon cancer is common, affecting mostly older people. Since age is a risk factor, young patients might not be given the same attention as older ones regarding symptoms that could imply the presence of colon cancer. **Objectives:** To investigate whether young patients, i.e., under age 50, complain of symptoms for longer than older patients until the diagnosis of colon cancer is established. **Methods:** In this retrospective cohort study, patients were divided into two groups: < 50 years old (group 1) and ≥ 50 (group 2). All had undergone surgery for left or right colon cancer during the 10 year period of the study from January 2000 through December 2009 at one medical center. Rectal and sigmoid cancers were excluded. Data collected included age, gender, quantity and quality of complaints, duration of complaints, in-hospital versus community diagnosis, pathological staging, the side of colon involved, and overall mortality. The primary outcome was the quality and duration of complaints. Secondary outcomes were the pathological stage at presentation and the mortality rate. **Results:** The study group comprised 236 patients: 31 (13.1%) were < 50 years old and 205 (86.9%) were ≥ 50. No significant difference was found in the quantity and quality of complaints between the two groups. Patients in group 1 (< 50 years) complained for a longer period, 5.3 vs. 2.4 months ($P = 0.002$). More younger patients were diagnosed with stage IV disease (38.7% vs. 21.5%, $P = 0.035$) and fewer had stage I disease (3.2% vs. 15.6%, $P = 0.06$); the mortality rates were similar (41.9% vs. 39%). Applying a stepwise logistic regression model, the duration of complaints was found to be a predictor of mortality ($P = 0.03$, OR 1.6, 95% CI 1–3.6), independently of age ($P = 0.003$) and stage ($P < 0.001$). **Conclusions:** Younger patients are more often diagnosed with colon cancer later, at a more advanced stage. Alertness to patients' complaints, together with evaluation regardless of age but according to symptoms and clinical presentation are crucial. Large-scale population-based studies are needed to confirm this trend.

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KEY WORDS: colonic neoplasm, diagnosis, advanced staging, young age, duration of symptoms

Colorectal cancer is the third most common cancer in both men and women, with more than 140,000 new cases diagnosed each year in the United States (101,000 colon, 39,000 rectum). In Israel about 3200 new cases are diagnosed each year. According to the American Cancer Society, lifetime risk for developing CRC is 1 in 19 (5.2%), and expected deaths exceed 50,000 per year [1]. The mortality rate for CRC has decreased over the last 20 years, mostly due to meticulous screening programs and early detection. Age is an established risk factor; 90% of those affected are above age 50 years, and the incidence continues to rise until age 75. Only 0.1% of all CRCs are diagnosed in patients under 20 years old, and 1% in those aged 20 to 34. Although younger patients tend to present with advanced-stage disease more commonly than older patients, it is not clear whether, stage for stage, the prognosis differs from that of older patients [2,3]. Factors found to be associated with increased risk to develop CRC include: personal history of colorectal polyps or colorectal cancer, personal history of inflammatory bowel disease, familial history of CRC, obesity, physical inactivity, tobacco use, heavy alcohol use, low fiber diet, and high consumption of red meat [4–13]. The present study was initiated to examine whether young patients are given the same attention as older patients regarding symptoms that could imply the presence of colon cancer. We feel that patients and physicians tend to underestimate symptoms in young patients and do not act as promptly to establish a diagnosis when suspicious symptoms present.

PATIENTS AND METHODS

This was a retrospective study of all patients admitted from January 2000 through December 2009 to the Department of General Surgery at the Rambam Health Care Campus, Haifa, with a proven diagnosis of colorectal cancer. Only patients who underwent their index procedure (colectomy) with a diagnosis of adenocarcinoma at this medical institution were included. Patients with rectal or sigmoid cancer were excluded from the study because clinical presentation and tumor biology vary substantially between the different tumors and therefore a possible

bias was eliminated [14]. Patients included in the study were either diagnosed in community clinics or after admission to the hospital. The primary aim of the study was to investigate whether younger patients, under age 50 years, diagnosed with colon cancer complain of symptoms for a longer period than those who are older. Once a longer duration of complaints was established, a secondary aim was to investigate whether this affects the pathological stage at diagnosis and the mortality rate.

Data collected included age, gender, and type and duration of complaints prior to diagnosis as revealed in the history of disease presented upon admission to the department of surgery. Also recorded was the side of colon involved, the pathological stage according to the Union for International Cancer Control [15], whether surgery was elective or urgent, where the diagnosis was made (community versus in-hospital), and mortality. All admissions to the hospital were performed by general surgery residents or interns and were all based on computerized standardized electronic charts. Patients were divided into two groups: patients under 50 years old (group 1), and patients aged 50 and above (group 2). All variables were compared between the two age groups.

The Institutional Review Board of Rambam Health Care Campus approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

STATISTICAL ANALYSIS

Mean, standard deviation, range, and frequencies were used as descriptive statistics and analyzed by the Student *t*-test. The Mann-Whitney U test was used to analyze the duration of complaints. The linear by linear association chi-square test was applied to analyze data by running the SPSS for windows (version 17.0) statistical package. A stepwise logistic regression model was applied to assess the impact of duration of complaints on the outcome of patients controlling for confounding factors. *P* < 0.05 (two-sided) was considered to indicate statistical significance.

RESULTS

The study included 236 patients. Mean age was 71.5 ± 14.3 years, 124 (52.5%) were male, and 140 (59.3%) suffered from left-sided colon cancer. The mean duration of complaints prior to diagnosis was 1.8 months. Mean follow-up was 3.6 years. Overall mortality was 39.4%. The most common symptom, abdominal pain, presented in 51.3% of patients, followed by change in bowel habits in 41.5% and weight loss in 32.6%. Table 1 presents the symptoms according to pathological stage, as assessed by the Union for International Cancer Control.

The cohort of patients was divided into two groups, group 1 (< 50 years old) comprising 31 patients (13.1%), and group 2 (≥ 50 years) 205. Table 2 presents demographic data and the symptoms in the two groups. No statistically significant differences were found in the quantity and quality of com-

Table 2. Comparison of characteristics and symptoms between the two age groups

	Group 1 < 50 yr (n=31)	Group 2 ≥ 50 yrs (n=205)	P value
Age (yr)	41.4 ± 7	71.9 ± 10.2	0.0001
Male gender (%)	48.4	53.7	0.7
Side of malignancy (left) (%)	47.9	71.0	0.14
Pain (%)	64.5	49.3	0.13
Diarrhea (%)	16.1	10.2	0.35
Constipation (%)	29.0	29.3	1.00
Vomiting (%)	19.4	10.2	0.14
Weight loss (%)	29.0	33.2	0.84
Rectal bleeding (%)	25.8	19.0	0.47
Melena (%)	0.0	3.4	0.60
Change in bowel habits (%)	51.6	40.0	0.24
Duration of complaints (mon)	5.3	2.4	0.002
Overall survival (%)	58.1	61.0	0.84

Table 1. Symptoms related to pathological stage in the complete cohort of patients

Stage	Abdominal pain % (n)	Diarrhea % (n)	Constipation % (n)	Vomiting % (n)	Weight loss % (n)	Rectal bleeding % (n)	Melena % (n)	Change in bowel habits % (n)
1	30.3 (10)	9.0 (3)	33.3 (11)	3.0 (1)	33.3 (11)	24.2 (8)	3.0 (1)	33.3 (11)
2a	62.8 (44)	15.7 (11)	28.6 (20)	15.7 (11)	31.4 (22)	15.7 (11)	2.8 (2)	48.6 (34)
2b	66.6 (2)	0.0 (0)	0.0 (0)	33.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
3a	45.4 (5)	9.0 (1)	18.2 (2)	9.0 (1)	27.3 (3)	0.0 (0)	0.0 (0)	9.0 (1)
3b	44.1 (15)	8.8 (3)	23.5 (8)	2.9 (3)	17.6 (6)	14.7 (5)	2.9 (1)	29.4 (10)
3c	37.0 (10)	3.7 (1)	37.0 (10)	11.1 (3)	25.9 (7)	37 (10)	0.0 (0)	55.5 (15)
4	60.3 (35)	12.1 (7)	31.3 (18)	12.1 (7)	48.3 (28)	22.4 (13)	5.2 (3)	46.5 (27)
Total	51.3 (121)	11 (26)	29.2 (69)	11.4 (27)	32.6 (77)	19.9 (47)	2.9 (7)	41.5 (98)
Pvalue	0.01	0.75	0.71	0.26	0.03	0.16	0.93	0.03

Figure 1. Progressive decline of mean duration of complaints with age. The plot bars describe the mean duration of complaints in each age while the black line shows the average over time

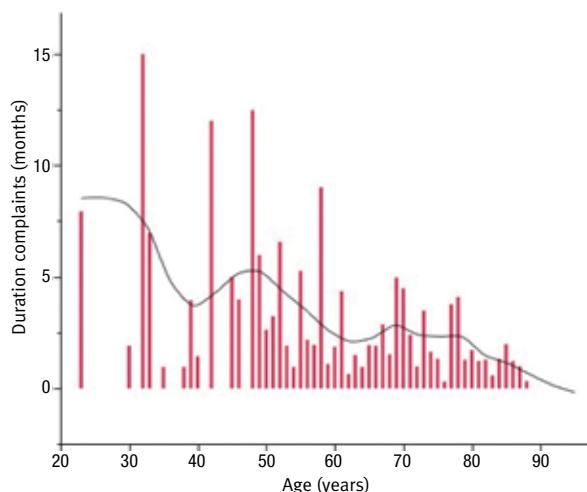


Table 3. Pathological staging in the two groups

Stage % (n)	Group 1 (n=31)	Group 2 (n=205)	Pvalue
1	3.2 (1)	15.6 (32)	0.06
2a	29.0 (9)	29.3 (60)	0.85
2b	3.2 (1)	1.0 (2)	0.34
3a	0.0 (0)	4.9 (10)	0.37
3b	12.9 (4)	14.1 (29)	1.00
3c	12.9 (4)	10.24 (21)	0.75
4	38.7 (12)	21.5 (44)	0.035

plaints between the groups. The duration of complaints prior to diagnosis was significantly longer in group 1 compared to group 2: 5.3 vs. 2.4 months respectively ($P = 0.002$). Figure 1 shows the progressive decline in duration of complaints with the advancement of age.

The distribution of pathological stages for the two groups is presented in Table 3. Group 1 showed 3.2% (n=1) stage I colon cancer, compared to 15.6% in group 2 (n=32) ($P = 0.06$). Stage 4 disease was diagnosed more in group 1 than in group 2: 38.7% (n=12) vs. 21.5% (n=44) ($P = 0.035$) [Table 3].

As previously mentioned there was no difference in overall survival of the two groups (log rank test, $P = 0.92$), and no difference was detected when compared only to patients with node-positive stages. On a multivariate analysis using a stepwise logistic regression model, duration of complaints was found to be a significant independent predictor of mortality ($P = 0.03$, odds ratio 1.6, 95% confidence interval 1–3.6) independently of age ($P = 0.003$) or stage of disease ($P < 0.001$). The odds ratio implies that for every month longer

that a patient complains he/she has a 1.6-fold higher chance of dying.

DISCUSSION

Colon cancer is a preventable disease. Primary and secondary prevention are possible and readily available. Screening programs have succeeded in reducing the incidence of colon cancer by early diagnosis and detection of premalignant lesions. The 5 year survival rate increased from 52% in 1975 to 66% in 2006, mostly due to national screening programs, risk factor reduction and new effective treatments [3,16]. One normal colonoscopy may reduce the lifetime risk for colon cancer by 31% and a subsequent colonoscopy by 80% [3]. As paramount as screening is, once symptoms present, timely referral to the appropriate medical discipline for diagnosis and treatment is of utmost importance since early diagnosis is the cornerstone of curative treatment.

Previous studies have reported the age-related differences in colon cancer: young patients present higher rates of distal tumors [17,18] and higher rates of node-positive disease and poorly differentiated tumors [17,19–21]. Although debatable, Morris et al. [17] showed that young patients present different molecular features of tumors with higher rates of microsatellite instability and TP-53, and lower rates of BRAF and K-ras mutations. Unlike other reports, the current study highlights the presenting symptoms of patients with colon cancer, the length of patients' complaints, and the relation to disease stage at diagnosis and prognosis.

In the current study we used 50 years as the cutoff age for the two groups since the prevalence of colon cancer is shown to increase significantly above this age [3]. The two age groups showed homogeneity with regard to gender. Furthermore, and more importantly, younger and older patients complained of the same symptoms at similar frequencies. However, the duration of complaints prior to diagnosis was significantly longer in the younger patients (5.3 vs. 2.4 months, $P = 0.002$).

A number of reasons may explain the difference in symptom duration between the age groups, such as the prevalent, yet erroneous disbelief that cancer is not likely to present in this age group and the consequent tendency to ignore the presenting symptoms. More importantly, a patient presenting to a physician may easily be dismissed with a benign diagnosis without sufficiently evaluating the possibility of malignancy due to the physician's same erroneous assumption.

Once a late diagnosis was established, we explored whether the longer duration of complaints had an impact on the patient's outcome. We found that the younger patients (group 1) had significantly more diagnoses of stage 4 colon cancer (38.7% vs. 21.5%, $P = 0.03$) but fewer diagnoses of stage 1 colon cancer (3.2% vs. 15.6%, $P = 0.057$). It is well documented that stage of

disease is the single most important predictor of outcome, and the higher rates of stage 4 disease should have a grave impact on outcome. However, when we compared the survival curves of the two groups no difference was detected (log rank test, $P = 0.92$) overall or when comparing node-positive patients only. In order to adjust for possible common confounders, we performed a multivariate analysis using a stepwise logistic regression model, adjusting for age and stage. We found that duration of complaints was an independent predictor of mortality. The importance of the duration of complaints cannot be underestimated as evidenced by our results, which show that for every month longer of complaints the patient has a 1.6-fold chance of dying.

Unfortunately, the retrospective nature of the study as well as different sites of follow-up obviate proper evaluation of the cause of death, hence the limited ability to draw firm conclusions.

CONCLUSIONS

Although uncommon, colon cancer may present at a young age. It seems that younger patients are more often diagnosed late, at a more advanced stage. The results of this study show unequivocally that prompt referral and consequent diagnosis is of utmost importance. While promoting awareness of colon cancer by large-scale campaigns is important, alertness to patients' complaints, together with evaluation regardless of age but according to symptoms and clinical presentation are crucial. Large-scale population-based studies are needed to confirm this trend.

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References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59 (4): 225-49. Epub 2009 May 27.
- Ryan DP, Engelman JA, Ferrone CR, Sahani DV, Lisovsky M. Case records of the Massachusetts General Hospital. Case 19-2010. A 35-year-old man with adenocarcinoma of the cecum. *N Engl J Med* 2010; 362 (25): 2411-19.
- Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
- Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990; 323 (18): 1228-33.
- Ziogas A, Horick NK, Kinney AY, et al. Clinically relevant changes in family history of cancer over time. *JAMA* 2011; 306 (2): 172-8.
- Friedenreich C, Norat T, Steindorf K, et al. Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2006; 15 (12): 2398-407.
- Wolin KY, Lee IM, Colditz GA, Glynn RJ, Fuchs C, Giovannucci E. Leisure-time physical activity patterns and risk of colon cancer in women. *Int J Cancer* 2007; 121 (12): 2776-81.
- Slattery ML. Physical activity and colorectal cancer. *Sports Med* 2004; 34 (4): 239-52.
- Morikawa T, Kuchiba A, Yamauchi M, et al. Association of CTNNB1 (beta-catenin) alterations, body mass index, and physical activity with survival in patients with colorectal cancer. *JAMA* 2011; 305 (16): 1685-94.
- Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA* 2008; 300 (23): 2765-78.
- Giovannucci E. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* 2002; 31 (4): 925-43.
- Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 2006; 119 (11): 2657-64.
- Zbuk K, Sidebotham EL, Bleyer A, La Quaglia MP. Colorectal cancer in young adults. *Semin Oncol* 2009; 36: 439-50.
- Kapiteijn E, Liefers GJ, Los LC, et al. Mechanisms of oncogenesis in colon versus rectal cancer. *J Pathol* 2001; 195 (2): 171-8.
- Union for International Cancer Control, TNM Classification of Malignant Tumors. 7th edn. New York: Springer, 2009.
- Itah R, Greenberg R, Werbin N, Sacham-Shmueli E, Inbar R, Avital S. Current changes in the management and outcome of patients with curable colorectal cancer. *IMAJ Isr Med Assoc J* 2011; 13 (5): 300-3.
- Morris M, Platell C, Iacopetta B. A population-based study of age-related variation in clinicopathological features, molecular markers and outcome from colorectal cancer. *Anticancer Res* 2007; 27 (4C): 2833-8.
- Gonzalez EC, Roetzheim RG, Ferrante JM, Campbell R. Predictors of proximal vs. distal colorectal cancers. *Dis Colon Rectum* 2001; 44 (2): 251-8.
- Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. *Br J Surg* 2003; 90: 205-14.
- Lin JT, Wang WS, Yen CC, et al. Outcome of colorectal carcinoma in patients under 40 years of age. *J Gastroenterol Hepatol* 2005; 6: 900-5.
- O'Connell JB, Maggard MA, Livingston EH, Yo CK. Colorectal cancer in the young. *Am J Surg* 2004; 187: 343-8.

Capsule

Spreading depression triggers headache by activating neuronal Panx1 channels

The initial phase in the development of a migraine is still poorly understood. Karatas and fellow researchers describe a previously unknown signaling pathway between stressed neurons and trigeminal afferents during cortical spreading depression (CSD), the putative cause of migraine aura and headache. CSD caused neuronal Pannexin1 (Panx1) megachannel opening and caspase-1 activation followed by high mobility group box 1 (HMGB1) release from neurons and nuclear factor κB activation in astrocytes. Suppression

of this cascade abolished CSD-induced trigeminovascular activation, dural mast cell degranulation, and headache. CSD-induced neuronal megachannel opening may promote sustained activation of trigeminal afferents via parenchymal inflammatory cascades reaching glia limitans. This pathway may function to alarm an organism with headache when neurons are stressed.

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