



Research Article

Diagnostic Relevance of Primary Investigations in Early Referral and Management of Colorectal Cancer Patients

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Abstract

Aim: Colorectal cancers are largely considered as curable yet the high mortality rates associated with it points out at deficiency in early management of the disease. The aim of this study was to analyze the diagnostic potential of routine primary investigations with an attempt to categorize symptoms for early referral of colorectal cancers patients.

Methods: This study involved retrospective analysis of a cohort of 85 patients diagnosed with colorectal cancer that underwent surgery in a period of one year. The patients were arranged into different age-groups to analyze the relative incidence and prognosis of the disease with respect to generalized symptoms and clinicopathological details. Multinomial Logistic Regression analysis was employed to predict the most effective set of parameter combinations for primary prognosis of the diseased state.

Results: Abdominal pain, rectal bleeding and change in bowel habits were predominantly reported symptoms; however, these were imprecise with age, sex or stage of cancer. Interestingly, almost 85% of the patients were reported anemic, with a majority of them (41.7%) having Hb < 10. Anaemic patients showed significantly higher frequency of symptoms viz. change in bowel habits ($p < 0.023$), rectal bleeding ($p < 0.035$) and/or abdominal pain ($p < 0.039$) compared to non-anaemic ones. The co-occurrence of any two of the symptoms further increased the likelihood of the disease in anaemic patients.

Conclusion: A substantial decrease in hemoglobin count with concomitant change in bowel habits, rectal bleeding, and/or abdominal pain could be considered as potential referral markers for early management of suspected colorectal cancers patients.

Keywords: Referral markers in colorectal cancer; Anaemia; Rectal bleeding

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Introduction

Colorectal cancer is the third most common cancers claiming over 6 million lives every year [1,2] with over 2.5 million deaths annually in asian subcontinent alone [2]. Despite being much curable and preventable [1, 3], the higher mortality rates points towards deficiencies in early prognosis and management of the disease. Although, there have been remarkable advances in medical diagnostics from past few decades, yet commonly practiced medical procedures are largely unable to diagnose early stage colorectal cancers putting large number of patients at risk of developing advanced stage cancers. There is an immediate need to address the deficiencies in clinical diagnostics at primary level to overcome or restrict cancer related deaths. In this study, we analyzed generalized symptoms associated with colorectal cancers and the efficacy of routine clinical investigations with an aim to stress upon the need for detailed examination of patients with clinically relevant symptoms of colorectal cancer.

Methods

Study Design: The study was carried out on a cohort of 85 patients referred for surgical resection of the tumor growth of the colon. The patients were examined by routine procedures viz. Digital rectal examination (DRE), Proctosigmoidoscopy, Colonoscopy and Contrast Enhanced Computed Tomography (CECT) besides general check-up before being operated upon. Serological analyses include blood CEA levels, WBC count, hemoglobin estimation etc. Biopsies of the colonic lesions were sent to pathological laboratory for detailed examination.

Patient grouping: For analyzing the relative

incidence and clinicopathological details, patients were grouped in five age-groups: Group 1 (< 30 years); Group 2 (31-45 years); Group 3 (46-60 years); Group 4 (61-70 years) and Group 5 (> 70 years). For MLR analysis, patients were grouped according to state of haemoglobin (anaemic/non-anemic).

Data analysis: Clinicopathological data were collected from all the patients as per institutional ethical guidelines. The data were stratified by patient symptoms, primary investigations and clinical findings, and compared across all the age-groups. Surgical observations were also collected at the time of surgery for comparison. The outcome of the clinicopathological variables were summarized as percentage of patients bearing the symptom/state within the specified group. Multinomial logistic regression (IBM® SPSS® v.22) was used to compare chief complaints/symptoms associated with anaemic patients compared to non-anaemic subjects. Differences were considered statistically significant at $p < 0.05$.

Results

Incidence rates and generalized symptoms: Based upon the clinicopathological data, the incidence rates were calculated using age, sex, demography or smoking history [Table 1]. Most of the patients were aged between 46-60 years (34.12%), followed by 61-70 (21.18%), 31-45 (20%), 16-30 (16.47%) and > 70 (8.24%). Except patients below 30 years of age, the Male: Female ratio was higher (> 1) across all the age groups. The primary investigation reports compared across all the age-groups revealed majority of patients with symptoms viz. abdominal pain, rectal bleeding or change in bowel habits across all the groups [Table

2].

Clinical investigations vs Surgical findings: Histologically, almost all the patients (94.44%) were diagnosed for adenocarcinoma [Table S1]. More than 48% of the patients were diagnosed with advanced grade tumors [Moderately differentiated + poorly differentiated CRC], however, symptoms viz. abdominal pain, rectal bleeding, change in bowel habits were equally prevalent irrespective of tumor grade [Table S2]. Four critical parameters were analyzed in clinical and surgical reports to ascertain the efficacy of clinical diagnosis related to tissue damage or stage of cancer: 1) Breaching of abdominal serosa by cancerous cells; 2) Lymph node involvement; 3) Accumulation of intestinal fluids; and 4) Liver metastasis. Surgical observations revealed much advanced cancers which were reported less invasive type by clinical examinations [Table S3], which could be a consequence of delay in the surgical procedure.

Carcinoembryonic antigen (CEA) levels: Serological levels of CEA were analyzed across the age-groups or cancer types; however, these were entirely indecisive to correlate with onset, progress or grade of cancer [Table S4]. Values below 2.5 ng / ml were considered as normal.

Hemoglobin count: Analysis of the clinical reports of patients showed that about ~85 percent of the patients were anemic [Hb: < 12.1g/dl (Females) < 13.8g/dl (Males)]. The anemic patients outnumbered non-anemic ones across all age-groups. A scale based analysis of hemoglobin count showed that almost 42% of the patients (19.05% males; 22.62% females) had Hb values less than 10g/dl, 23.81% (11.90% males; 11.90% females) had Hb values between 10-11 g/dl and 14.29% (3.57% males; 10.71% females) had Hb values of 11-12g/dl [Table 3]. Anemic condition followed a regular trend with the type/grade of cancer, being more prominent in early grade compared to advanced grade cancers [Table 4].

Table 1 Details of patients registered in the study

Age Group	16-30		31-45		46-60		61-70		>70	
	%	n	%	n	%	n	%	n	%	n
No. of Patients	16.47	14	20	17	34.12	29	21.18	18	8.24	7
Average Age (Yrs)*	26.06 ± 5.54		40.23 ± 4.14		54.82 ± 4.57		66.16 ± 3.13		76.42 ± 3.69	
Gender										
Females	71.43	10	41.18	7	34.48	10	44.44	8	42.86	3
Males	28.57	4	58.82	10	65.52	19	55.56	10	57.14	4
Residence										
Urban	21.43	3	23.53	4	44.83	13	50.00	9	57.14	4
Rural	78.57	11	76.47	13	55.17	16	50.00	9	42.86	3
Smoking history										
Smokers	14.29	2	47.06	8	41.38	12	38.89	7	71.43	5
Ex/Non-Smokers	85.71	12	52.94	9	58.62	17	61.11	11	28.57	2

* Data expressed as Average age ± SD

Table 2 Primary investigations reports of the patients with Colorectal cancers.

Age Group	16-30		31-45		46-60		61-70		>70	
	+	-	+	-	+	-	+	-	+	-
General Symptoms										
Abdominal Pain	71.43	28.57	58.82	41.18	68.97	31.03	44.44	55.56	42.86	57.14
Intestinal Swelling	14.29	85.71	29.41	70.59	6.90	93.10	11.11	88.89	28.57	71.43
Anaemia	85.71	14.29	94.12	5.88	89.29	10.71	77.78	22.22	100	-
Bleeding PR	57.14	42.86	52.94	47.06	68.97	31.03	77.78	22.22	71.43	28.57
Change in Bowel Habits	78.57	21.43	70.59	29.41	68.97	31.03	77.78	22.22	100	-
Distension	7.14	92.86	17.65	82.35	6.90	93.10	11.11	88.89	14.29	85.71
Generalized Weakness	50.00	50.00	23.53	76.47	27.59	72.41	55.56	44.44	-	100
Pallor	57.14	42.86	47.06	52.94	58.62	41.38	44.44	55.56	28.57	71.43
Tenderness	7.14	92.86	11.76	88.24	3.45	96.55	11.11	88.89	14.29	85.71
Clinical findings										
Co-morbidity	7.14	92.86	29.41	70.59	53.57	46.43	55.56	44.44	85.71	14.29
Past History of any Cancer/ pre-cancerous growth	-	100	-	100	3.45	96.55	-	100	-	100
Synchronous Lesions	22.22	77.78	-	-	3.45	68.97	21.43	78.57	-	100
Serosa Breached	50.00	50.00	41.18	58.82	34.48	65.52	44.44	55.56	57.14	42.86
Lymphadenopathy	50.00	50.00	70.59	29.41	51.72	48.28	55.56	44.44	57.14	42.86
Ascites	-	100	5.88	94.12	6.90	93.10	-	100	14.29	85.71

Data obtained from patient registry and includes reports based upon DRE, Proctosigmoidoscopy, Colonoscopy and CECT. Values are expressed as relative percentage with the specified group (s); (+) sign indicates presence of the specified variable, (-) sign indicates its absence.

Table 3 Hemoglobin variations in unit scale

	<10g/dl	10-11g/dl	11-12g/dl	12-13g/dl	13-14g/dl	>14g/dl
Males	19.0	11.9	3.6	7.1	4.8	1.2
Females	22.6	11.9	10.7	4.8	1.2	1.2
Overall %age	41.7	23.8	14.3	11.9	6.0	2.4

Data expressed as relative percentage of patients.

Table 4 Hemoglobin variations with grade of cancer

Status of Hemoglobin	Tumor Grade		
	WD	MD	PD
Normal	11.8	3.5	0.0
Anaemic	40.0	29.4	15.3
Total	51.8	32.9	15.3

Data expressed as relative percentage of patients. WD: well differentiated; MD: Moderately differentiated; PD poorly differentiated.

Multivariate analysis: Using Multinomial logistic regression (IBM® SPSS® v.22) analyses, change in bowel habits, rectal bleeding, or abdominal pain were rendered as potential symptoms associated with anaemia in colorectal cancer patients compared to non-anaemic patients. Change in bowel habits showed significant coherence with anemic state (OR = 2.139, $p = 0.023$), followed by abdominal pain (OR = 1.664, $p = 0.035$) and rectal bleeding (OR = 1.299, $p = 0.039$) [Table 5]. A concurrent presence of any two of these symptoms *viz* change in bowel habits, rectal bleeding, or abdominal pain further enhanced the likelihood of the disease in anaemic patients compared to non-anaemic patients.

Table 5 MLR estimates of chief complaints associated with anaemia in colorectal cancer patients

Hemoglobin state ^a	Odds ratio Exp(B)	95% Confidence Interval for Exp(B)		P value
		Lower Bound	Upper Bound	
		Anaemic		
Change in Bowel Habits	2.139	0.051	0.186	0.023
Bleeding PR	1.664	0.041	0.170	0.035
Abdominal Pain	1.299	0.025	0.167	0.039
Change in Bowel Habits + Bleeding PR	2.603	0.042	0.115	0.021
Change in Bowel Habits + Abdominal Pain	2.421	0.043	0.185	0.026
Bleeding PR + Abdominal Pain	1.310	0.052	0.171	0.029

a. The reference category is: Non-anaemic.

Discussion

Colorectal cancers tend to continue as the third most commonly found cancers [9], with mortality rates of ~ 8% [9, 10] owing to late detection or poor prognosis of the patients [11, 12]. Colorectal cancers develop gradually with the formation of non-cancerous “*polyp*”. The transformation of “*polyps*” into adenomas may go undetected till advanced stage cancers resulting in severe mortality. The adenomas growing at the intestinal lining may alter intestinal secretions or invade blood vessels giving typical symptoms of the colon cancer viz bowel disturbances, rectal bleeding, abdominal pain etc. However, the onset of these symptoms may not always be correlated with stage or severity of cancer as is evident from the disagreements between clinical and surgical findings highlighted in this report, which could only be attributed to the delay in advanced referral of the patients [13]. Clinicians are now engaged to ascertain the diagnostic value of symptoms associated with colorectal cancer in primary care [4, 14] alone to allow better referral investigations for these patients [15]. The symptoms associated with colorectal cancer have been described in numerous clinical studies [5-7], together with their estimated risks. A study by Hamilton *et al* (2005) reported a strong association between incidence of colorectal cancers and severity of anaemia [8], while other studies held the argument insensitive [16]. Our study records a strong prevalence of colon cancers associated with low hemoglobin levels coupled with the characteristic symptoms viz rectal bleeding change in bowel habits and abdominal pain, supporting the importance of primary investigations in colon cancers. Furthermore, this study recommends a prompt referral of patients to advanced care once the patients are admitted with complaints of anaemia, rectal bleeding, and change in bowel habits and/or abdominal pain. Additionally, this type of a pilot

study highlighted non-age relatedness of anaemia with risk of developing colorectal cancers and could possibly encourage further research in clinical association of hemoglobin deficiency and cancers; besides it could also help to review current referral of patients in primary care.

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Appendices: See supplementary material

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