ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 10, Issue – 1, February – 2025, Page No. : 01 – 11

Clinical and Treatment Profile with Five Year Survival Analysis of Colorectal Cancer from Himalayan State of India

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Citation this Article: Kaushal Singh Rathore, U.K. Chandel, Niharika Singh, Sudershan Sharma, Lalita Negi, "Clinical and Treatment Profile with Five Year Survival Analysis of Colorectal Cancer from Himalayan State of India", IJMSIR - February – 2025, Vol – 10, Issue - 1, P. No. 01 – 11.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: The incidence of colorectal cancer (CRC) is increasing worldwide. Middle- and low-income countries are also experiencing increases in these cases. This is attributed to their large and rapidly growing populations coupled with the adoption of westernized diets and lifestyles.

Methods: All diagnosed cases of colorectal cancer presenting to IGMC, Shimla (the sole tertiary cancer care centre in the state of Himachal Pradesh, India) within the study period of January 2017 to December 2018 were included. Data on the clinical characteristics, pathology, treatment received, and survival outcomes were recorded. A Kaplan–Meier estimation of survival, defined as the time from presentation to death, was conducted within the follow-up period of 60 months (last follow-up 31st December 2023).

Results: The study included 165 patients, with a male predominance, mean age of 56.8 years, and 34% aged <50 years. The most prevalent symptoms were anorexia and weight loss (97%), and the rectum was the most common site (42%). Histopathological signet ring-type morphology was observed in 15% of the cases, and the majority of patients presented with advanced stages III (36%) and IV (32%). Radiation oncologists, surgeons, and medical oncologists employed a multimodal treatment approach. After 60 months of follow-up, 22 patients were lost to follow-up and only 23 remained alive. Kaplan–Meier analysis revealed that clinical stage was a significant factor for survival, with a five year survival of 31%.

Conclusion: Most patients presented at an advanced stage with a significantly young population, which not only resulted in complex management but also poor

survival outcomes. Further epidemiological studies, including genetic analyses, are necessary to characterize the presentation of colorectal cancer in our state.

Keywords: Colorectal cancer, clinicopathological and treatment profile, follow up, multimodality treatment.

Introduction

Colorectal cancer (CRC) are second most common cause of cancer related deaths worldwide and as per incidence they are third most common in both sexes [1]. There is a global rise in both the incidence and prevalence of CRC, which is more evident in low- and middle-income countries; however, when we examine data from high-income countries, especially those that have implemented screening programs, it seems to be stabilized [2]. CRC rates are increasing in India and currently account for the seventh most common cancer in both sexes, with almost 80-90% of cases diagnosed in patients aged >50 years [3]. In a recent update from the United States Multi-Society Task Force (MSTF), the screening age for average risk was reduced to 45 years because of the increased disease burden in the <50 years age group [4]. The rise in incidence in low- and middle-income countries can be attributed to the increased prevalence of obesity and altered dietary patterns, with increased consumption of fast food and red meat and lower consumption of dairy products. There is approximate 2-4 times rise in the incidence of CRC in many Asian countries over the last two decades [5]. The global prevalence of CRC in the <40 years age group is approximately 2-3%, but reports from India show that its prevalence is much higher [6]. The clinical presentation of CRC is diverse, ranging from altered bowel habits, bleeding per rectum, anemia, and generalized weakness to surgical emergencies due to perforation, obstruction, and bleeding. Although the hospital-based cancer registry (HBCR) has inherent selection bias but in scarcity of population-based cancer registries (PBCRs) in the Himalayan region of India, this epidemiological data is an important source of information for understanding the pattern of disease in the region. This study aimed to investigate the clinicopathological and treatment profiles of patients with CRC presenting in this tertiary care center over a period of two years period, with a secondary endpoint of 5-year survival.

Methodology

This prospective observational study was conducted in the Department of General Surgery in coordination with the Department of Pathology and Radiation Oncology at Indira Gandhi Medical College (IGMC), Shimla, Himachal Pradesh, which is the only regional cancer center for the entire state of Himachal Pradesh. Prospectively all the patients presenting with colorectal cancer from January 2017 to December 2018 were included. Patients who refused to provide consent and those with recurrence were excluded. A prospective database of colorectal cancer was created to record data pertaining to demographics, clinical profile, investigations, histopathology, staging, treatment details, and survival outcomes. All patients were evaluated with respect to detailed history and physical examination and were investigated to confirm the diagnosis and stage of the disease. The study tools included a study questionnaire, investigations [routine blood tests, colonoscopy, USG, CECT, and MRI], and histopathological reports. The parameters studied were age, sex, site of lesion, clinical presentation, histopathology of the lesion, stage of disease, treatment received and five-year survival.

Treatment

All the patients received treatment according to the clinical stage of the disease. Resection was considered

curative if there was no preoperative evidence of metastasis and there was R0 resection as per the histopathological report. All other resections were considered to be palliative. Standard long-course neoadjuvant chemoradiotherapy for locally advanced rectal carcinoma rectum and 5-Fluorouracil–based adjuvant chemotherapy were advised according to the institutional guidelines.

Follow up

All patients were followed-up from the hospital visit, and yearly, all patients were telephonically called, and complete details of their health were documented. If a patient died, the date of death was recorded by their relatives. The last follow-up was conducted on December 31, 2023.

Statistical analysis

All statistical analyses were performed using SPSS software (version 21.0, SPSS Inc., Chicago, IL, USA), and numerical data are expressed as mean, median, range, frequency, and percentage. Categorical variables are presented as frequencies and percentages. Overall survival included the time from the month of diagnosis to the month of death, regardless of cause; the last follow-up was on 31st December, 2023. Patients lost to follow-up were excluded, and Kaplan–Meier curves were drawn. Statistical differences in the observed survival curves were analyzed using the log-rank test. For all analyses, a p-value of < 0.05 was considered statistically significant.

Definition of variables

Age at diagnosis was the presenting age of the patient to IGMC, Shimla, Age <40 years was defined as young-onset CRC, and age > 40 years was defined as late-onset CRC. The Asian-Pacific BMI classification was used to define nutritional status; BMI <18.5 was malnourished and >23 was obese. The past occurrences of CRC in family members, including spouses, first-degree relatives (brothers/sisters, children, parents), and second-degree relatives (half-brothers/half-sisters, grandchildren, grandparents), are said to have a positive family history. AJCC 8 was used to determine clinicopathological variables (7). The 2019 World Health Organization (WHO) guidelines were used to determine the histological grades (8), From the cecum to the transverse colon considered right side, splenic flexure to the rectosigmoid was considered the left side and beyond into the rectum; those patients who did not turn up for follow-up or did not follow the treatment plan were considered defaulters.

Results

CRC patients constitute 165 of a total of 4548 cancer patients (3.5%), and it constitutes the fifth most common cancer in men and sixth in women, according to our institutional cancer database. The number of patients presenting with colorectal cancer increased with age, and 110(66%) patients were aged > 50 years, with a mean age of presentation of 56.8 years and a range of 21-91. CRC incidence in the young population was 26(16%) (Table 1). There was a male predominance in 92 (55.75%) patients, and the most common risk factor was a non-vegetarian diet (taking non-vegetarian meals > 3 times a week) in 124 (75%) patients, followed by smoking in 89 (54%) patients. Constitutional symptoms, such as anorexia and significant weight loss (>10% of body weight in the last 3 months), were the most common presenting symptoms observed in 160(96%) patients with anemia (hemoglobin <12 g/dl) and bleeding per rectum being second and third (Table1).

On comparing the location of the tumor, the rectum was the most common site observed in 69(42%) cases, and the most common histopathological grade was well-differentiated adenocarcinoma seen in around 65(40%) patients, with signet type seen in 24(15%) patients

(Table2).A significant number of patients presented with metastasis 52(32%), with the most common site of metastasis being the liver 32(19.39%), followed by the lung 23(13.93%) and peritoneum 13(7.87%)(Table 2).Most of the patients presented to us had higher stages (stage III + IV), constituting approximately 111(67%) (Table 2).A total of 113 patients underwent curative surgery, with the open approach being the most common 87(52.72%), while the laparoscopic approach was used in 16(14%) patients. The patients who underwent curative resection in the emergency setting were 10(6.06%). Long-term neoadjuvant chemoradiotherapy was administered to 36(22%) patients, palliative surgeries in the form of ileostomy/colostomy/palliative resection were performed in approximately 14(8.48%) patients, and palliative chemotherapy was administered to 52(32%) patients, with CAPOX/FOLFOX as the first-line treatment (Table 2).A significant number of patients were defaulters 82(50%), and most were advised to receive adjuvant chemotherapy 52(31.51%), followed by palliative chemotherapy 30(18.18%).All patients who were advised to receive long-course neoadjuvant chemoradiotherapy, completed the intended therapy.

At the end of the follow-up, 22(13%) patients were lost to follow-up, and 23(14%) were alive (Table 3). Overall 5 year survival was 31%, and none of the patients with stage IV disease survived for five years (Table 3).The median overall survival of all stages was calculated as 48 months, with the highest survival at 80 months in stage 1(Table 4). The survival of patients who received curative multimodal treatment was 57 months, compared to those who received palliative treatment at 25 months(Table 5).Kaplan–Meier curves showed that patients who underwent curative treatment had significantly better survival than those who received palliative treatment ($p<0.001$), and survival significantly decreased as the stage of the disease increased ($p<0.001$) (Figures 2 and 3).Twenty-two patients were excluded from the survival analysis because they were lost to follow-up.

Discussion

According to the GLOBOCAN 2022 estimates, the most common newly diagnosed cancer worldwide is lung cancer (12%), and CRC is the third most common cancer worldwide (9%). The incidence at our institute is 3.5%, which is similar to the national average [1]. Our hospital is the largest and only tertiary care cancer center in the state with regional referrals. The mean age at initial diagnosis was 56.8 years (range-21-91 years, which is higher from an Indian study by Patil et al, 47.2 years [9] and similar to studies from Saudi Arabia, 57.9 years [10] and Singapore,52.7 years [11]). Age is regarded as a significant risk factor for the development of CRC, as most cases were seen after 50 years 110(66%). CRC in < 50 years was approximately 35%, which is a matter of concern, and it is considerably higher than the West (7 %) [12], but it is similar to a report from India (30-35%) [13]. The cause of increased CRC in young individuals remains unknown, apart from genetic, environmental, and dietary factors, and the major reason in India is its growing population with a broad pyramid. According to the 2011 census, 62.5% of the population lies between the age group of 15-59 years unlike the West, which has a larger elderly population. Currently, there is no recommendation for CRC screening in India and there is no standardization of national data. However, in the near future, India will require screening guidelines to match the pace at which CRC incidence is rising, and issues pertaining to young people, such as psychosexuality, fertility, quality of life (QOL), and long-term effects of therapy in India, should be addressed in more detail.

In our study, CRC was observed more frequently in men than in women, with a ratio of 1.26:1, which is similar to a study from another Himalayan state, Kashmir 1.5:1, and from the USA stating 30-40% more CRC in male than in female [14,15].The majority of CRC patients were non-vegeterians 124(75%), smokers 89(54%), and consumed alcohol 80(49%), which was similar to a study from Indonesia that showed a high association between smoking/non-vegetarian diet and CRC [16].Obesity is linked to the development and progression of CRC, but our study had a majority of malnourished patients 90(54.5%), similar to a study from Saudi Arabia [17].

The presentation of CRC varies from asymptomatic (detected on screening colonoscopy) to emergency hospitalization with perforation, obstruction, and gastrointestinal hemorrhage. According to a retrospective cohort study of > 29,000 patients, the most common presentation was a change in bowel habits and bleeding P/R [18]. In our study, the most common presenting symptoms were anorexia and weight loss (>10% of body weight in 3 months) and anemia (observed in 160(97%) and 135(82%) patients, respectively). Bleeding per rectum was observed in a significant number of patients 91(55%), mostly rectal carcinomas. Upon retrospectively asking leading questions, it was found that a large number of patients 140(85%) had altered bowel habits, most of whom ignored these symptoms, took traditional medications and local treatment, and presented to us when the disease advanced, which clearly reflected the low education and awareness of CRC in our population.

Similar to a previous study [14], the most common site was the rectum, 69 (42 %) with synchronous lesions in nine (5.5%) patients. The most common histopathological type [19] was adenocarcinoma 160(97%), but a significant number of patients had signet ring cell type morphology 24(15%) compared to the West, where it is reported to be around 1-2% [20].

Most patients presented with Stage III 59(36%)and stage IV disease (n = 52, 32%); only nine (5%) presented with Stage I disease, which is similar to the findings of Kumar et al. [21] and Amin et al. [22] from Saudi Arabia. Due to the advanced stage of presentation, treatment not only becomes more complex but also more morbid, longer in duration, and causes increased cost and burden on our health care system. The most common site of metastasis was the liver 32(19%), followed by the lungs 23(13%).

Multimodality treatment was offered to patients according to stage: 113(69%) underwent curative surgery, including laparoscopic surgery in 16(10%) and emergency surgery in 10(6%) patients; approximately 14 out of 24 patients who presented in the emergency setting underwent palliative surgery, which included formation of diversion stoma in 10 and palliative resection in 4 (in view of tumor perforation and fecal peritonitis); 36(22%) patients (ca rectum) received neoadjuvant chemoradiotherapy; and palliative chemotherapy was administered to 52(32%) patients [23].

5 year overall survival rate was 31%, similar to a recent study from Rwanda [24] and lower than the national average [9] and developed Asian countries [20].On comparing of 5 year survival rate between our study and the Western study [25] showed a striking difference in stages I (88 vs. 92), II (83 vs. 87), III (7 vs. 72), and IV (0 vs. 12), which could be due to the high rate of defaulters, financial constraints, illiteracy, lack of awareness, poor quality of surgical specimens with inadequate clearing of lymph nodes, poor nutritional status, lack of targeted therapy according to genetic analysis, and unknown inherent genetic factors that cause poorly differentiated/signet-morphology cancers that are also present in the young population. There is general

consensus in our region that surgery is the only way to prolong life in cancer so it was seen when we advised neoadjuvant therapy, every patient followed our advice but when it came to adjuvant or palliative setting there were many defaulters.

The National Comprehensive Cancer Network (NCCN) recommends genetic testing, such as multigene panels, for patients diagnosed at <50 years of age, and approximately 15% of patients have deficient mismatch repair genes that influence prognosis and response to fluorouracil [26]. The median overall survival (OS) was 48 months. There was a significant difference between the median survival of treated patients with respect to palliation (57 vs. 25 months ($p<0.001$), with stage appearing to be a significant predictor of overall survival ($p<0.001$) [23].

The limitations of this study were its small sample size, descriptive approach, and non-evaluation of factors other than clinical stage that could affect survival, as it is the first data from our Himalayan state in India with a large follow-up. We hope that this study can prove to be useful for program and policy formation in India, in an effort to reduce not only the number of patients but also the mortality rate as seen in Taiwan, where after the introduction of a nationwide screening program, a reduction in mortality of 15% between 2014-17 [27]

Table 1: Clinico-demographic profile of colorectal cancer patients

Parameters	Number of patients (n)	Proportion of patients (%)
Gender		
Male	92	55.75
Female	73	44.25
Age group (years)		
<40	26	15.75
>40	139	84.24
Co Morbidity		
Hypertension	13	7.87
Diabeties Mellitus	12	7.27
Body Mass Index(BMI)		
<18.5 (Malnourished)	90	54.5
18.5-23(Normal)	41	24.84
>23(obese)	34	20.60
Risk factor		
Smoker	89	53.93
Alcohol	80	48.48
Non-Vegeterian	124	75.15
Family History	1	0.60
Presenting complaints		
Pain abdomen	89	53.93

Lump Abdomen	41	24.89
Bleeding P/R	91	55.15
Anaemia*	135	81.81
Anorexia and weight loss$	160	96.96
Altered bowel habbits	140	84.84
Emergency#	24	14.5

*Anaemia – Haemoglobin <12 g/dl, $ anorexia and weight loss >10 % of body weight in last 3 months, #emergency presentation as intestinal obstruction and perforation.

Table 2: Pathological and treatment profile of colorectal cancer patients

Tumor Location		
Right	58	35.15
Left	29	17.57
Rectum	69	41.81
Synchronous	9	5.45
Histopathology		
Well differentiated*	65	39.39
Moderately differentiated*	55	33.33
Poorly differentiated*	16	9.69
Signet ring cell type	24	14.54
Others	9	3.03
Clinical Stage		
I	9	5.45
II	45	27.27
III	59	35.75
IV	52	31.51
Metastasis		
Liver	32	19.39
Lung	23	13.93
Peritoneum	13	7.87
Other	6	3.63
Treatment Modality		

Curative Surgery (laparoscopic/ open/emergency)	113(16/87/10)	68.48(9.69/52.72/6.06)
Adjuvant chemotherapy	104	63.03
Neoadjuvant chemoradiotherapy	36	21.81
Palliative chemotherapy	52	31.51
Palliative Surgery	14	8.48
Defaulters	82	49.69

*Adenocarcinoma

Table 3: Follow up and one/three/five-year survival

Stage	Number	Lost to follow up	1 year (%)	3 year (%)	5 year (%)
All stages	165	22	93	81.81	30.76
I	9	1	100	100	87.5
II	45	3	100	100	83.33
III	59	13	97.8	86.95	6.52
IV	52	5	82.97	51.06	0

Table 4: Overall survival according to clinical stage (months)

Stage	Total N	Death	Alive	Mean Survival	Median Survival	95% CI For Median	P Value
1	8	2	6	77.81	80.0	80 - NA	Log Rank Test: p = <0.001
2	42	25	17	69.15	67.0	65 - NA	
3	46	46	0	44.65	46.5	43 - 51	
4	47	47	0	22.13	25.0	19 - 28	
1+2+3+4	143	120	23	45.13	48	41.65-48.62	

Table 5: Overall survival between treated and palliative patients

Stage Category	Total N	Death	Alive	Mean Survival	95% CI for Mean	Median Survival	95% CI For Median	P Value
1/2/3	96	73	23	58.39	54.81 - 61.97	57	54 – 63	Log Rank Test: p = <0.001
4	47	47	0	22.13	19.67 - 24.59	25	19 - 28	

Figure 1: Overall survival of Colorectal cancer (CRC) patients (months)

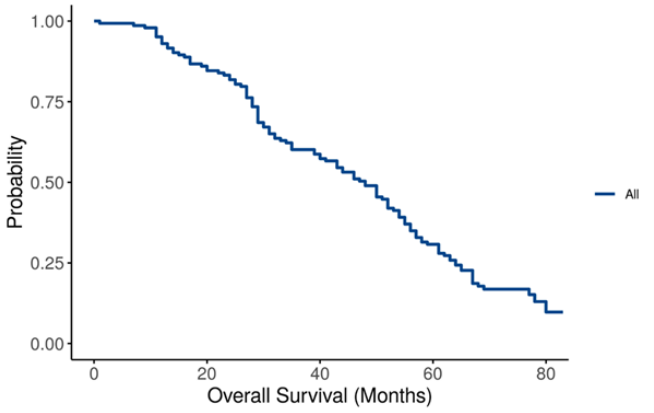

Figure 2: Survival comparison between treated and palliative patients

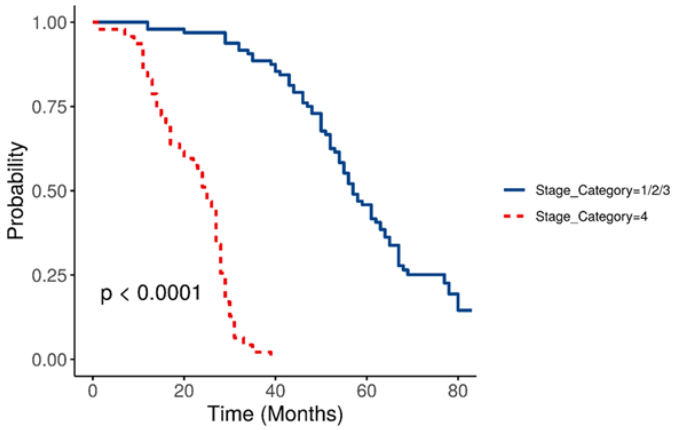

Figure 3: Survival of Colorectal cancer patients according to clinical stage

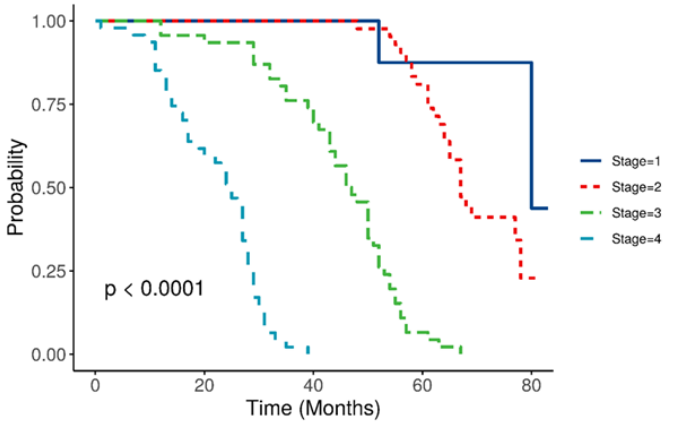

Figure 4: Raincloud plot showing survival of Colorectal cancer patients according to stage

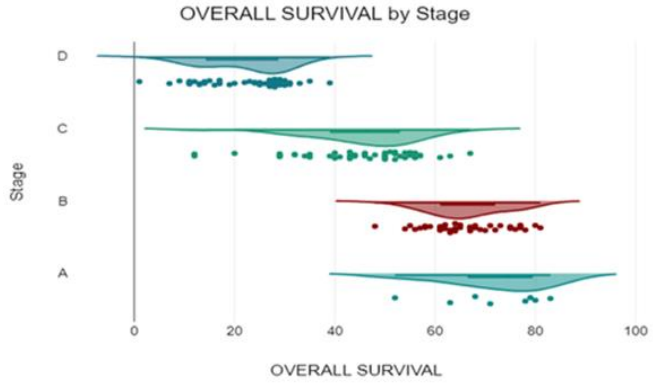

Figure legends

1) Kaplan Meyer curve depicting overall survival of patients in months , patients who were alive on 31st December were censored.
2) Kaplan Meyer curve depicting overall survival of patients in months , patients who were alive on 31st December were censored. A-stage I+II+II survival, B- stage IV survival, p<0.001(significant)
3) Kaplan Meyer curve depicting overall survival of patients in months, patients who were alive on 31st December were censored. Stage A-I, B-II, C-III, D-IV, p<0.001(significant).
4) Raincloud plot showing the overall survival according to clinical stage A-I, B-II, C-III, D-IV in months. It clearly demonstrates inverse relation between stage and survival.

Conclusion

Altered bowel habits and bleeding per rectum are common presenting symptoms of CRC, which are usually missed by patients and even overlooked by family physicians. There is a need for an hour to educate people to not take these symptoms on a lighter note. Colorectal cancer is not limited to the older population. Its incidence has been increasing in the young population, which has been shown to present late with poor differentiation/signet cell morphology. Due to the

rising population in low- and middle-income countries with the adoption of a Westernized diet, its prevalence is increasing at a rapid rate, and there is a dire need for screening programs for colorectal cancer. These programs must be framed such that they consider the psychosexual needs of the young population. Owing to a lack of awareness, most patients present late, and the lack of available healthcare facilities makes survival poor in these countries.

Abbrevation: CRC- Colorectal cancer, HBCR - hospital-based cancer registry, QOL-quality of life

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