

Five Year Survival Analysis of Colon Cancer: A Retrospective Study

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survival probability dropped drastically stage IIIB onwards with Mayo clinic protocol. The five year survival with only surgery was 90% in stages I and II. Median survival of patients who developed metastasis to liver was about 20 months. Those who also had ascites besides secondary liver, median survival reduced to 12 months.

CONCLUSION: Mayo clinic protocol is a simple, effective and affordable alternative to FOLFOX 4 protocol up to stage IIIA colon cancer, especially suitable for peripheral settings.

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Key words: Colon cancer; Survival analysis; Mayo clinic; FOLF-
OX4

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ABSTRACT

AIM: Various chemotherapy protocols, both cheap and costly are available for treatment of colon cancer. This study was carried out to analyze the five year survival probability with different protocols.

METHODS: A total of 415 patients attending our oncology OPD from January 2002 to December 2008 who had biopsy-proven colon cancer were retrospectively accrued in this hospital based study. 65% patients were male. The patients were stratified according to treatment received (surgery and adjuvant chemotherapy), age wise and stage wise. Statistical comparison of different adjuvant chemotherapy protocols was performed on the basis of different age groups and stage using Kaplan Meier method. All statistical calculations were performed using Medcalc software for windows, version 12.5.0 (Osterd, Belgium).

RESULTS: Five year survival probability with FOLFOX 4 protocol was 85% while with Mayo clinic protocol, it was 80% ($p=0.0071$). In all stages (except stage IV) and age groups (except >70 years), FOLFOX-4 protocol yielded above 80% five year survival ($p<0.0001$). Mayo clinic protocol gave comparable results till stage IIIA. However,

INTRODUCTION

Colorectal cancers (CRC) account for nearly 10% of all cancers worldwide. It is the third most common cancer in men and second most common in women^[1]. Studies have shown that risk of CRC increases with age with peak incidence above the age of 70 years^[2]. The United Nations defines a country as "Ageing" or "Graying Nation" where the proportion of people over 60 reaches 7% to total population. By 2001 India has exceeded that proportion (7.47%) and is expected to reach 12.6% in 2025 with improving life expectancy^[3]. Furthermore, studies have suggested higher incidence rates of CRC in Indian immigrants to the United Kingdom and USA^[4-6]. This finding can be explained in terms of changed life styles and dietary habits of this population. At the same time, India is undergoing transition from a low income to middle income economy. These data clearly indicate the risk of increase in burden of CRC in Indian scenario. This is also confirmed by population based time trend studies^[7]. Surgery has been the mainstay of treatment in CRC. However, with a potentially curative surgery alone, up to 50% patients will ultimately relapse and die of metastatic disease^[8].

The prognosis of colon cancer patients has greatly improved in

last two decades with the use of 5-fluorouracil (5FU)/leucovorin (LV) based adjuvant chemotherapy. The bolus 5FU/LV regimen popularly known as Mayo clinic protocol and weekly bolus 5FU/LV known as Roswell Park regimen have remained reference regimens for adjuvant chemotherapy. There has been increasing use of oxaliplatin and irinotecan and they have improved the survival of metastatic colorectal cancer patients. Though many studies have compared various adjuvant chemotherapy regimens worldwide, there is great lack of similar data in Indian perspective. Also there is considerable importance of use of simpler and cheaper regimens in a developing country especially in peripheral settings. We present the findings of a retrospective hospital based study comparing five year survival of colon cancer patients treated by surgery alone or surgery with different adjuvant chemotherapy regimens.

METHODS

A total of 415 patients attending our oncology OPD from January 2002 to December 2008 who had biopsy-proven colon cancer were retrospectively accrued in this hospital based study. 65% patients were male. The patients were stratified according to treatment received (surgery and adjuvant chemotherapy), age and stage. Colon cancer was defined by the presence of the inferior margin of the tumor above the peritoneal reflection. The patients who had not received any prior chemotherapy and had adequate blood counts, liver and kidney functions were considered for adjuvant chemotherapy. Written informed consent was obtained from all patients before starting treatment. Adjuvant chemotherapy was started within eight weeks after surgery. The FOLFOX4 regimen consisted of oxaliplatin, 85 mg/m², given as a 2-hour infusion in 500 mL of dextrose 5% on day 1; LV, 200 mg/m²/day given as a 2-hour infusion, followed by a bolus 5-FU, 400 mg/m² and a 22-hour continuous infusion of 5-FU, 600 mg/m², repeated for 2 consecutive days. In diabetic patients, 500 mL of dextrose was neutralized with 7 units of regular insulin. Routine premedications were used at the commencement of chemotherapy. The cycle was repeated every 2 weeks. In patients receiving Mayo clinic regimen, intravenous bolus injections of LV 20 mg/m² and 5FU 400 mg/m² were given for 5 days without any premedications and cycle was repeated every 28 days.

Follow-up

Patients were assessed every two weeks during treatment, and then every three months for three years, then six monthly for next two years. During treatment, clinical history, physical examination, neurologic assessment in patients receiving oxaliplatin, complete blood count (CBC), liver and kidney function tests were assessed at baseline and were repeated every cycle. Serum carcino-embryonic antigen (CEA) level and contrast abdominopelvic computed tomography (CT) were assessed after six cycles. After completion of the chemotherapy, serum CEA level and chest radiography was performed every three months. Colonoscopy was done as indicated.

Statistical Calculations

Statistical comparison of different adjuvant chemotherapy protocols was performed on the basis of different age groups and stage using Kaplan Meier method and log-rank test. Overall survival at the end of five years of starting of treatment was the primary end point of study. Data were entered into Microsoft excel spreadsheet and subsequently imported into Medcalc software for windows, version 12.5.0 (Osterd, Belgium) for statistical calculations.

RESULTS

415 patients were enrolled in this retrospective study visiting our oncology OPD from January 2002 to December 2008. Table 1 shows the stage wise distribution of the enrolled patients with respect to the protocol received. Age and sex wise distribution of the patients is depicted in table 2. 36 patients (8.6%) underwent surgery only with no adjuvant treatment. 105 (25.3%) were given Mayo clinic protocol while 162 (39%) received FOLFOX4 regimen as adjuvant chemotherapy. 26 (6.2%) were given cisplatin and 5-FU while 86 patients (20.7%) who presented with advanced stage and poor performance status were kept on best supportive care. Five year overall survival probability with FOLFOX 4 protocol was 85% while with Mayo clinic protocol, it was 80% ($p=0.0071$) (Figure 1).

Figure 2 depicts the survival plots with Mayo clinic regimen (a) and FOLFOX4 (b) with respect to age groups of the patients. With Mayo clinic regimen, five year overall survival probability in the

Table 1 Stage wise distribution of patients on the basis of treatment received.

S. No.	Stage	Total	Treatment received				
			Only Surgery	Mayo clinic	FOLFOX4	Cisplatin+5FU	Best supportive care
1	I	15	7	4	1	3	0
2	II	169	24	51	80	14	0
3	IIIa	52	3	28	16	5	0
4	IIIb	38	0	9	27	2	0
5	IIIc	32	0	8	23	1	0
6	IV with surgery	23	2	5	15	1	0
7	IV without surgery	86	0	0	0	0	86
8	Total	415	36	105	162	26	86

Table 2 Age & sex wise distribution of patients according to protocol received.

S. No.	Age group (years)	Only surgery			Mayo clinic			FOLFOX4			Cisplatin+5FU			Best Supportive Care		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
1	20-29	3	1	4	4	1	5	3	3	6	2	0	2	0	0	0
2	30-39	5	6	11	8	5	13	12	4	16	4	3	7	1	1	2
3	40-49	6	2	8	9	5	14	17	8	25	3	1	4	2	1	3
4	50-59	3	2	5	11	8	19	42	17	59	4	2	6	7	6	13
5	60-69	4	2	6	24	20	44	40	15	55	3	1	4	10	4	14
6	70-79	2	0	2	6	1	7	1	0	1	2	1	3	28	71	45
7	>80	0	0	0	2	1	3	0	0	0	0	0	0	5	4	9
8	Total	22	14	36	64	61	105	115	47	162	18	8	26	53	33	86

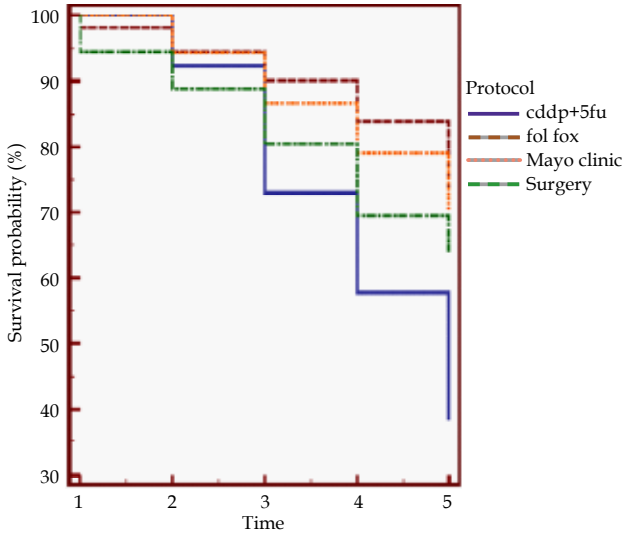
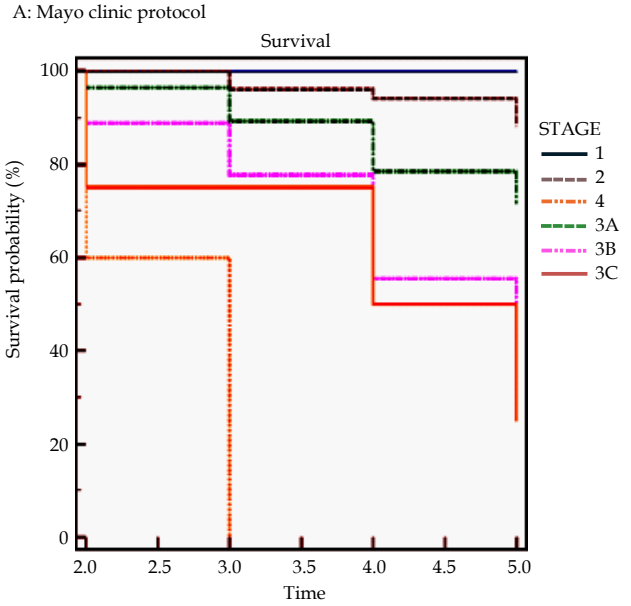
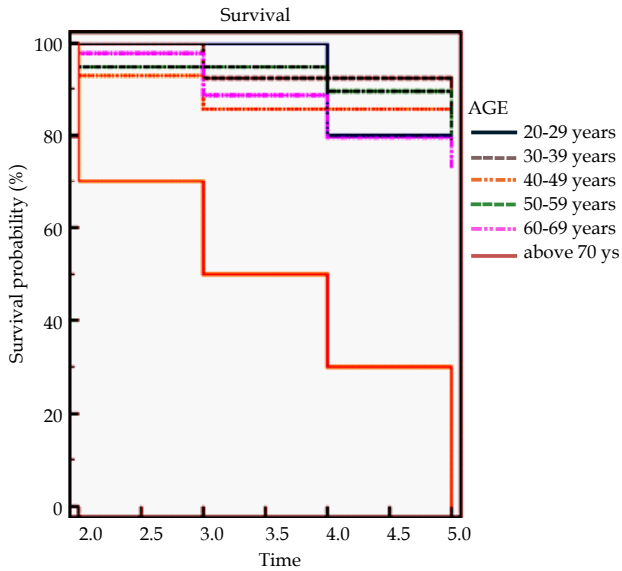


Figure 1 Kaplan-Meier Five Year Survival plot- Protocol wise.



A: Mayo clinic protocol

B: FOLFOX4 protocol



B: FOLFOX4 protocol

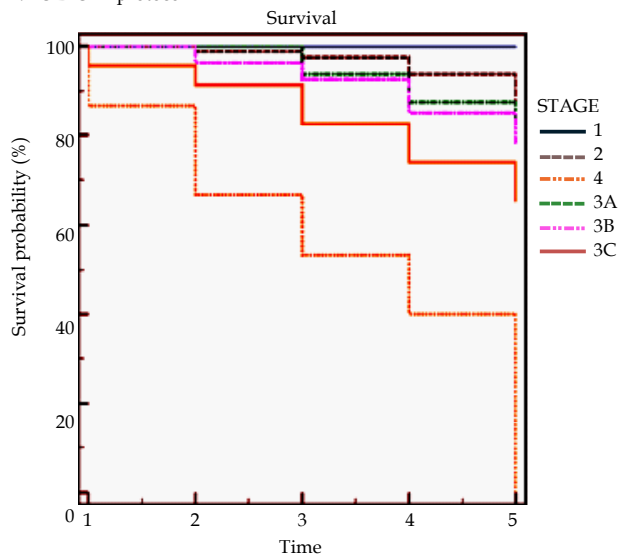


Figure 3 Kaplan-Meier Survival plots- Stage versus protocol received.

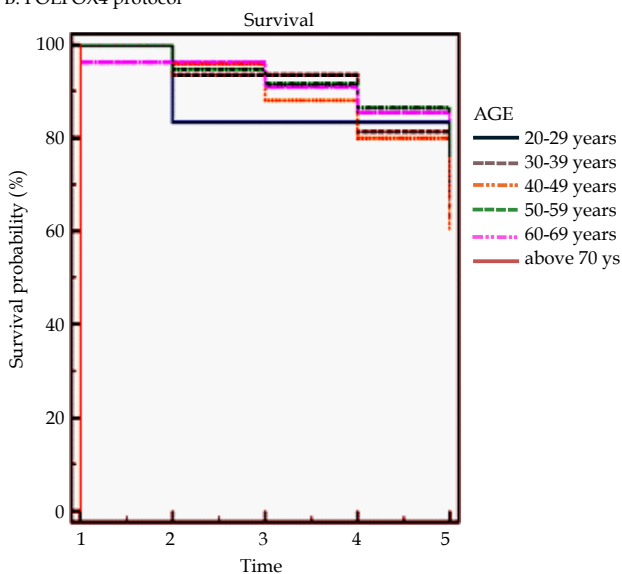


Figure 2 Kaplan-Meier Survival plots- Age group versus protocol received.

age groups 20-29 and 60-69 years was 80% while for 30-59 years, it ranged between 85-90%; >70 years group had three years survival probability of 50% but no patient survived till five years of starting the treatment ($p < 0.0001$). With FOLFOX4 protocol, the five year survival probability for 50-59 years was 90%, 0% for >70 years; for rest of the age groups, survival ranged between to 80-88%.

As shown in Figure 3, the five year survival probability with Mayo clinic and FOLFOX4 protocol in stage IIIA was 80% versus 90%; for stage IIIB, it was 55% versus 88% while for stage IIIC, it was 50% versus 75%, respectively. Both protocols yielded 95% survival in stage II. However, three year survival with FOLFOX4 protocol was 50% while no patient could survive till three years with Mayo clinic regimen ($p < 0.0001$). The five year survival with only surgery was 90% in stages I and II. No patient of stage III and IV could survive till five years who refused adjuvant treatment after surgery. Median survival of patients who developed metastasis to liver was about 20 months. Those who also had ascites besides secondary liver, median survival reduced to 12 months.

DISCUSSION

Adjuvant chemotherapy given after a potentially curative surgery was developed for patients with stage II and III colon cancer to reduce the risk of disease relapse, both local and systemic. A traditional endpoint of adjuvant clinical trials for colon cancer has been 5-year Overall Survival (OS). Intergroup trial established 5FU and LV combination chemotherapy as the standard protocol for stage III colon cancer^[9,10]. The Multicenter International Study of Oxaliplatin/5FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial compared FOLFOX4 with infusion/bolus 5FU plus LV for resected stage II and III colon cancer^[13]. The disease free survival (DFS) at 3 years was 78.2% for the FOLFOX regimen versus 72.9% for the LV+5FU regimen. The FOLFOX4 regimen increased the probability that a patient would be alive and disease-free at 3 years by 5.3%. In this trial, the favorable effect in the subgroup of patients with stage III disease lead to the significant DFS and OS benefits in the overall FOLFOX group. For stage II patients, there was no statistically significant improvement in 5-year DFS or 6-year OS. The role of postoperative adjuvant therapy for stage II colon cancer still remains controversial, and the MOSAIC trial showed only a trend toward improved DFS at 5 years in patients with high-risk stage II disease treated with the FOLFOX4 regimen, as compared to patients treated with the LV+5FU regimen. The National Surgical Adjuvant Breast and Bowel Project 07 (NSABP-07) trial compared oxaliplatin and bolus 5-FU/LV (FLOX) regimen to the bolus 5-FU/LV (Roswell Park regimen) for resected stage II and III colon cancer and also demonstrated the superiority of an oxaliplatin-based regimen in the adjuvant treatment of colon cancer^[11]. Three-year DFS was 76.1% in the FLOX group compared to 71.8% in the FULV arm; compared to the FULV regimen, the FLOX regimen increased the probability that a patient would be alive and disease free at 3 years by 4.3%. The relative hazard of the DFS event was reduced by 20% with FLOX treatment as compared to FULV treatment, with a HR of 0.80 (95% CI, 0.69 to 0.93; $p=0.0034$). These data confirm that a significant DFS benefit can be attained when oxaliplatin is added to fluoropyrimidine-based regimens. Jeon *et al* reported the DFS and the OS rates at 3 years of 82.9% and 87.5%, respectively^[12]. In their study, 82 post operative colon cancer patients received FOLFOX4 or modified FOLFOX6. The disease-free survival rate at 3 years was 82.9%: 84.6% for stage II and 82.6% for stage III. At the time of the analysis, 8 patients were dead from recurrence. The probability of overall survival at 5 years was 74.5%: 90% for stage II and 74.6% for stage III.

Within our limits of diagnostic evaluation facilities, we considered OS as an end point for our study as DFS estimation was not possible in most of the patients. In our study, use of FOLFOX4 regimen lead to 85% five year survival probability up to stage IIIC. With Mayo clinic protocol, five year survival probability was 80% in stage IIIA and it dropped to 60% in stage IIIB and 30% in stage IIIC. Thus, maximum benefit of costly FOLFOX4 protocol over simpler and cheaper Mayo clinic regimen was obtained in stage IIIB and IIIC. Thus, the trends suggest that Mayo clinic regimen is almost as good as FOLFOX4 up to stage IIIA in terms of five year OS; at the same time lower toxicities are expected from this simpler protocol. The updated results of the MOSAIC trial showed a trend toward improvement in survival for patients treated with the FOLFOX regimen^[13]. The DFS rates at 5 years were 73.3% for the FOLFOX regimen and 67.4% for the LV+5FU regimen (HR, 0.80; 95% CI, 0.68 to 0.93; $p=0.003$). The OS rates at 6 years were 78.5% for the FOLFOX regimen and 76.0% for the LV+5FU regimen (HR, 0.84; 95% CI, 0.71 to 1.00; $p=0.046$).

Adjuvant oxaliplatin, 5FU and LV chemotherapy resulted in similar efficacy without significant increase in toxicity in older patients aged >65 when compared with younger patients with curatively resected Stage III colon cancer. Therefore, for colon cancer patients aged >65, oxaliplatin, 5FU and LV chemotherapy can be recommended as safe and effective adjuvant chemotherapy after curative surgery in Asia^[14].

The data for five year overall survival with use of different adjuvant chemotherapy regimens in our retrospective study are consistent with those in various indicating the effectiveness of FOLFOX4 in stage III colon cancer who have undergone a potentially curative resection. However, till stage IIIA, Mayo clinic regimen is a cheaper and easier to administer alternative to costly oxaliplatin containing protocol especially suitable for peripheral settings in a developing country. The trends observed in this study should be confirmed by larger prospective studies to establish robust data supporting use of Mayo clinic regimen over other complicated and toxic regimens in colon cancer.

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