

*Full Length Research Paper*

# The effect of using combination chemotherapy in colorectal cancer in India: A single institute survey

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The incidence of colorectal cancer in India is on upward swing due to the change in dietary habits. This study was done to evaluate the efficacy of two commonly used regimens. In this study, colorectal cancer patients treated with adjuvant chemotherapy from 1997 - 2001 were included and followed up for a period of five years. The efficacy of the commonly used regimens was compared in terms of five year disease free survival. The three and five year disease free survivals of 5-fluorouracil monotherapy regimen were 42 and 22%, respectively. The 5-fluorouracil + levamisole regimen had a disease free survival of 48 and 24% in stage B at three and five years respectively in stage B. In stage C, the disease free survival at three and five year were 22% and 10% in 5-fluorouracil treated group whereas it was 24 and 14% in 5-fluorouracil with levamisole treated group at similar time interval. We conclude that 5-fluorouracil + levamisole regimen had no added benefit in various stages of colorectal cancer in terms of disease free survival in our patients compared to 5-fluorouracil.

**Key words:** Adjuvant chemotherapy, disease free survival, 5-fluorouracil, 5-fluorouracil + levamisole.

## INTRODUCTION

Colorectal cancer accounts for 10 - 15% of all cancers and is the second leading cause of cancer related death in western countries though its incidence is less in Indian set up (Bleiberg et al., 2005). Incidence of cancer in male: female is 6.7:5.5 per 100, 000 population in India. Risk factors for the colorectal cancer are dietary habits and familial adenomatous polyposis (Libuti et al., 2005). Due to various reasons, the incidence of colorectal cancer is on increasing trend in India (Mohandas et al., 1999). Surgery is the primary modality for curative intent, and it varies according to the site of tumor like hemicolectomy (depending on right or left sided colon cancer) and abdominoperineal resection in colorectal cancer. Systemic chemotherapy plays a major role in various stages of colorectal cancer. Chemotherapy and radiotherapy have a clear role in adjuvant therapy and for symptom palliation in advanced disease (Terashima et al., 2007). There are various regimens instituted, in which 5-fluorouracil forms an effective chemotherapeutic drug

for this cancer, along with levamisole, leucovorin calcium, oxaliplatin, capecitabine, irinotecan combinations.

Despite recent advances in chemotherapeutic treatment, great numbers of deaths occur each year from the disease as well as due to the adverse effects of anticancer drugs. There are enough data regarding the efficacy of various regimens, used in different stages of colorectal carcinoma among western population (Moertel et al., 1999; Fancini et al., 1994; Cascinu et al., 1999). The risk factors in our patient population is different from the risk factors in western population, hence the efficacy (Mohandas et al., 1999). To best of our knowledge, there is lack of data about the efficacy and toxicity of the same in Indian patient population. Hence a study was planned to know the efficacy of commonly used adjuvant chemotherapeutic regimens in different stages of colorectal cancer in our hospital set up during 1997 - 2001.

## MATERIALS AND METHODS

Patients of either sex, diagnosed to have colorectal cancer based on histopathology were included in this retrospective study. The study was approved by the Kasturba Hospital Ethics Committee.

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**Table 1.** Showing patient characteristics (Values in parenthesis shows the percentage).

Patient characteristics		Number
Total number of patients		91
Male to female ratio		60:31
Age distribution (In years)	31 - 40	14(15.38)
	41 - 50	18(19.78)
	51 - 60	28(30.76)
	61 - 70	18(19.78)
	Miscellaneous	13(14.28)
Patients in different stages	Dukes B	62(68.13)
	Dukes C	29(31.87)

The study was conducted in Shri Shiridi Sai Saba Cancer Institute, Manipal (A wing of Kasturba Hospital, Manipal, India) which is a referral hospital for South Karnataka, neighbouring states such as Goa and northern districts of Kerala during 1997 - 2001. We have seen 304 patients of colorectal cancer of Dukes stage A, B, C and D (Bigas MAR et al., 2003). We have included 91 patients of Dukes stage B (62) and C (29%) in our study who completed one chemotherapy regimen and excluded patients of dukes stage A and D. The patients in either arms were comparable in terms of they are comparable with respect to age, stage and prognostic factors, dose duration of therapy. The patients in 5-FU monotherapy arm and received 500 mg i.v bolus for five days in a week. In the other arm, levamisole was given in a dose of 150 mg twice daily for three days during 5-FU administration. This cycle was repeated every 4 weeks for six month period in both arms. These patients were followed up for 5 years from the day of completion of chemotherapy. The necessary information such as staging of cancer (modified Astler-Coller Dukes system), type of adjuvant chemotherapy received were collected from the hospital medical records for each patient.

The toxicity status of the patient after receiving chemotherapy was inquired by writing self-addressed post card to the patient and patients attenders, if it was not available on case sheet.

Efficacy was evaluated by using three and five year disease free survival (DFS that is the length of time after treatment for a specific disease during which a patient survives with no sign of the disease) for the commonly used regimens such as 5-fluorouracil monotherapy (5-FU) and 5-FU + levamisole (5-FU+lev) as this regimen was commonly used in our hospital set up between 1997 - 2001. The selection of the treatment regimen was mainly based on staging, physician and patient preference.

#### Statistical analysis

Five year disease free survival, in various stages (B and C) as well as for various chemotherapeutic regimens (5-FU, 5-FU+lev) were calculated by using survival curves, which plot percent survival as a function of time using the method of Kaplan and Meier (Graph-pad Prism statistical software package). The percentage of survival were obtained by drawing a perpendicular line from X axis at the interval of 36 months (3 years) and 60 months (5 years) to the curve and drawing a horizontal line from that point to Y axis.

## RESULTS

In this study we have analyzed the data of 91 patients with colorectal cancer of stage B and stage C, who were

treated during and completed one chemotherapeutic regimen during 1997 - 2001.

These patients were chosen from the pool of 304 patients who had been diagnosed and treated during this same period. Rests of the patients were either of stage A, stage D or stage B and C who discontinued the treatment because of socio economical reasons. The patient demographic profiles were given in Table 1.

#### Efficacy of different chemotherapeutic regimens

We have analyzed the data of patients who have been treated in our hospital for colorectal cancer during 1997 - 2001. Three year and five year disease free survival was calculated and expressed in percentage. The three and five year disease free survival was 44 and 36% in stage B and 20 and 12% in stage C which was statistically significant (Figure 1,  $P < 0.04$ ). The three and five year disease free survival in 5-FU treated group of stage B patients was 42% and 32% respectively (Figure 2). The 5-FU + Levimazole combination had a disease free survival of 48% and 24% at three and five years respectively in stage B. There was no statistical significant difference between the two treatment groups even though little difference between the two groups ( $P = 0.065$  and  $0.085$  between 5-FU and 5-FU + lev at three and five years interval).

The disease free survival at three and five years in all the regimens was 20% and 12% respectively in stage C. Twenty two percent of patients treated with 5-FU were free from recurrence at three years and 10% were free of recurrence at five years. This was more or less same in 5-FU + levamisole treated patients with no statistically significant difference between the groups (Figure 3,  $P = 0.068$  and  $0.059$  between 5-FU and 5-FU + lev at three and five years interval).

## DISCUSSION

The selection of adjuvant chemotherapeutic regime for a particular patient depends on many factors like staging of the cancer, other treatment modalities received, the tolerability and affordability for a particular regime in a given set up. Substantial progress has been made in the identification of new forms of treatment for colorectal cancer (Saltz et al., 2000; de Gramont et al., 2000). Patients with metastatic disease are living twice as long as there were one decade ago. The use of adjuvant chemotherapy has increased the likelihood of cure by 30% among patients with stage III (Moertel et al., 1990) which is also called as Dukes stage C (Bigas et al., 2003). In the last decade 5-FU and leucovorin combination was used as the principle adjuvant chemotherapy regime for colon cancer of Stage III. Patients with stage II colon cancer (Dukes B (Table 2)) were encouraged to

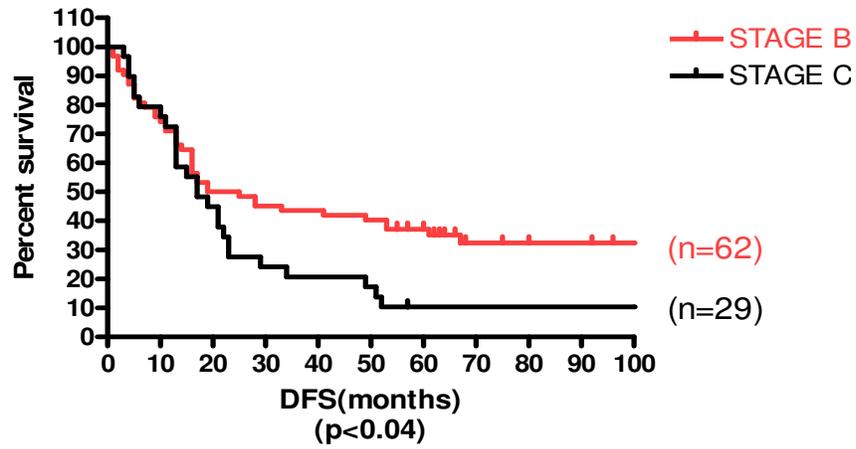


Figure 1. Stagewise disease free survival in different stages of colorectal cancer.

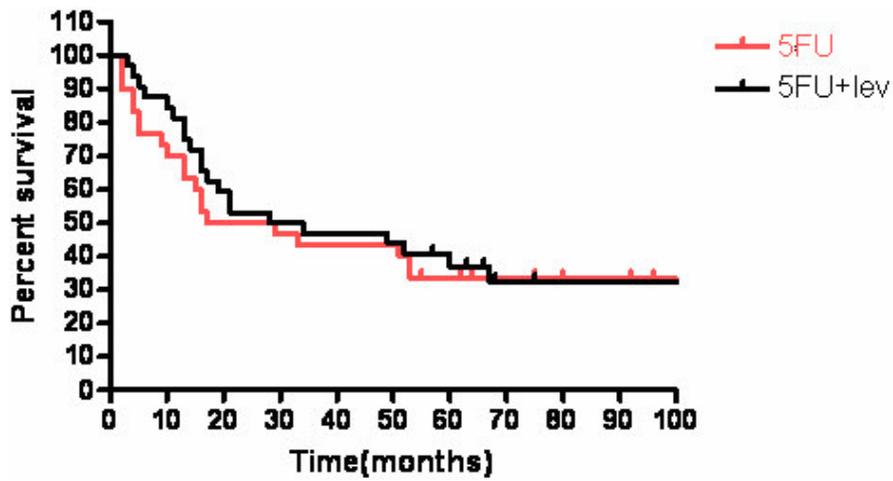


Figure 2. Disease free survival in stage B treated with two regimens. (P = 0.065 and 0.085 between 5-FU and 5 –FU + lev at three and five years interval)

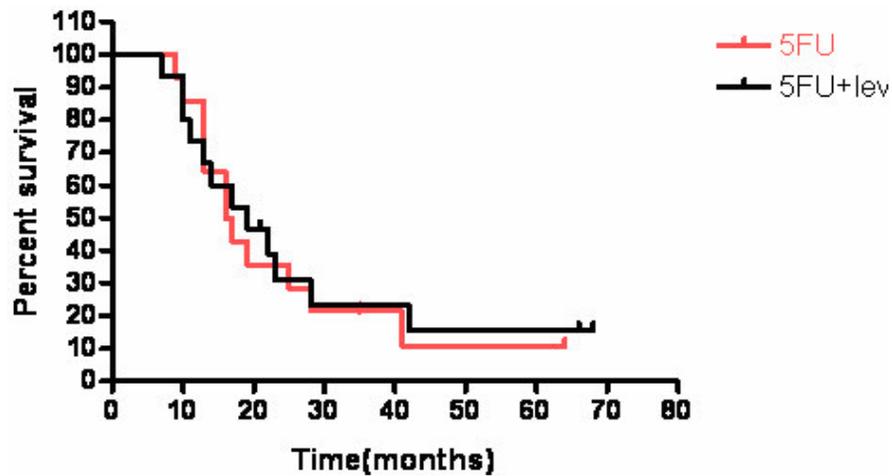


Figure 3. Disease free survival in stage C treated with two regimens. (P =0.068 and 0.059 between 5-FU and 5 –FU + lev at three and five years interval).

**Table 2.** Dukes classification of colorectal cancer.

Dukes stage	Features
Stage A	Tumor restricted to, but not through the bowel wall
Stage B	Penetration through the bowel wall
Stage C	Spread to the local lymph nodes
Stage D	Distant metastasis

participate in the on-going trials because adjuvant therapy has not yet proved to offer a survival benefit (Mamounas et al., 1999). For rectal cancers, post operative 5-FU based chemotherapy combined with irradiation should be the standard clinical approach for stage II and stage III disease because of its proven decrease in local recurrence, cancer related deaths and overall mortality (NIH Consensus Conference, 1990). In our hospital set-up oxaliplatin is incorporated in the adjuvant treatment of stage III so as the FolFox schedule now-a day. But our study included patients who have been treated during 1997 - 2001 period and followed up to 2006.

During that time, these regimens were just started showing positive results. We have not evaluated the efficacy of other regimens because of fewer numbers of cases. DFS after three years of median follow up is considered as an appropriate endpoint in colorectal cancer (Sergent et al., 2005). This can also be considered as surrogate to five year overall survival in colorectal cancer, hence we used this parameter to evaluate the efficacy of the above mentioned regimens (Charles et al., 2004). Various clinical trial groups have shown that addition of levamisole to 5-fluorouracil do not improve the recurrence rates even though immunostimulatory effect of levamisole was thought to enhance the therapeutic efficacy of 5-fluorouracil (Moertel et al., 1990; Fancini et al., 1994). The results were found to be better than our study. Some studies have shown that it is slightly better than 5 fluorouracil monotherapy (Cascinu et al., 1999). The reason given for the slight edge of the combination could be due to higher dose of 5-fluorouracil and the number of patients enrolled for the study in these trials (QUASAR Collaborative Group, 2000). In the stage B and stage C disease, the five years overall survival was found to be in the range of 70 - 80% and 35 - 60% respectively (Libuti et al., 2005). Our study has also revealed that the two regimens are more or less similar from efficacy point of view in terms of percent of disease free survival (three and five year disease free survival was 42 and 22% in stage B and stage C with 5-fluorouracil monotherapy and 48 and 24% in 5-fluorouracil combined with levamisole respectively). The recurrence rates are much higher in our patients (opposite of disease free survival) compared to QUASAR collaborative group.

We have not considered grading of the tumor, lymph vascular involvement and number of lymph nodes involved.

We think this has affected the outcome of the study. Had we randomized on these grounds, the efficacy could be near to the western literature. This was the weak link in our study. Since the efficacy data in our patient population with these regimens are lacking, this could be valuable in developing countries like India. We compared our results with the western literature because of the same reason.

The three common adverse effects seen with these groups were blood dyscrasia (28.05 vs. 22.99%), GIT manifestation in the form of nausea, vomiting, diarrhoea, constipation (23.17 vs. 25.29%) and LFT abnormalities in the form of elevated ALT, AST, hypoalbuminemia (23.17 vs. 25.29%) in 5-FU and 5-FU + Levamisole combination respectively. So we conclude by saying that 5-fluorouracil monotherapy is equally good as combination with levamisole. Larger sample size, randomization in terms of grading, lymphovascular invasion and nodal involvement could have thrown more information regarding the benefit of levamisole in the combination.

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