

Can we consider metastatic colon cancer in the ambit of chronic disease in present scenario? Experience of a tertiary care centre from India

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ABSTRACT

Background: Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and it is ranked the third most common globally. Nearly, one fourth of the CRC patients have metastasis at diagnosis and overall survival (OS) was not more than 6 months to 1 year. With availability of plethora of new chemotherapeutic drugs, biological agents and advent of newer techniques like radiofrequency ablation or hyperthermic intraperitoneal chemotherapy, it is possible to achieve OS of more than 2 years. **Materials and Methods:** A retrospective review of 105 case files of colon cancer was done, who were treated in our institute between January 2006 and December 2010. Patients with carcinoma colon were evaluated by a team of surgeons and radiation oncologists and underwent treatment according to the protocol designed by the same team. Only the histologically proven adenocarcinomas of colon were included. Out of 105 patients, 61 (58%) patients had metastatic disease either synchronous or metachronous and those patients were taken up for analysis. Various treatment modalities used in this group of patients in our setting were analyzed and correlated with progression-free survival (PFS) and OS. **Results:** This heterogeneous group of metastatic colon cancer patients, which had been given various modalities of treatment, could be able to achieve a median survival of around 18 months and 2 year PFS of 28%. **Conclusion:** So metastatic colon cancer is no longer an acutely fatal disease, rather it is in the ambit of chronic disease.

Key words: Chronic disease, metastatic colon cancer, chemotherapy, targeted therapy, radiofrequency ablation, hyperthermic intraperitoneal chemotherapy

INTRODUCTION

In 2012, colorectal cancer (CRC) continues to be a major public health problem. In the United States this year, there will be an estimated 147,000 new cases diagnosed and nearly 50,000 deaths resulting from this disease.^[1] Worldwide, approximately 1 million new cases of CRC are diagnosed each year, with nearly 500,000 deaths attributed to this disease annually. Fortunately, the age-adjusted incidence rates of CRC in all the Indian cancer registries are very close to the lowest rates in the world.^[2] Hospital-based and

population-based data also show that the incidence rates for rectal cancer is higher than colon cancer in all parts of India. Limited data from the rural population-based registries indicate that the incidence rates of colon cancer are very low in the rural settings. However, the incidence rates of rectal cancer is disproportionately higher in rural India.^[2,3] About 25% of patients present with metastatic disease, and of this group, 50-75% will have disease confined to the liver.^[4-6] In patients who present initially with early-stage disease, up to 50% will eventually develop metastatic disease, with the liver being the most common site. Another 10-20% of patients will present with disease involving the lung and other less common sites of metastatic involvement, including the peritoneum, ovaries, adrenal glands, bone, and brain.^[7,8] Approximately, 80% of patients with colorectal liver metastases present with unresectable disease at diagnosis. Recent reports have shown 5-year survival rates following resection of liver metastasis exceeding 50%. Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing

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surgery have been shown to be quite low in a number of studies.^[9,10] Fluorouracil has been the mainstay of treatment for metastatic CRC for a long time. However, in recent years, newer chemotherapeutic agents, particularly oxaliplatin and irinotecan have been shown to improve survival in combination with 5-fluorouracil (FU)-based therapies. The development of targeted agents that are tumor-specific with better toxicity profiles than chemotherapeutic agents has widened the spectrum of therapies for this disease. The two targeted agents, an antivascular endothelial growth factor monoclonal antibody bevacizumab and antibody against epidermal growth factor receptor (EGFR) cetuximab are effective agents in improving clinical outcome for patients with metastatic CRC. For patients who are unable to be cured by surgery, a combination of radiofrequency ablation (RFA) and regional chemotherapy has recently been introduced with encouraging results. The addition of RFA for patients treated with transarterial chemoembolization has recently been shown to improve overall survival (OS) in patients with unresectable CRC metastases to the liver. A growing field of interest has been the surgical management of peritoneal metastases from CRC, using cytoreductive surgery (CRS) and intraoperative chemoperfusion with mitomycin C or oxaliplatin, combined with hyperthermia (HIPEC) which had shown improvement in median survival when compared with systemic chemotherapy alone. Over the past 10 years, introduction of newer chemotherapeutic agents and novel-targeted agents, tremendous progress in the field of surgery and ablation therapies, the median survival of patients with advanced metastatic disease has gone from 10-12 months to nearly 24 months culminating metastatic CRC as a chronic disease. Keeping this in mind, we have conducted a retrospective analysis of our patients of metastatic colon cancer treated in last 5 years.

MATERIALS AND METHODS

A retrospective review of 105 case files was done, who were treated in our institute between January 2006 and December 2010. Patients with carcinoma colon were evaluated by a team of surgeons and radiation oncologists and underwent treatment according to the protocol designed by the same team. Only the histologically proven adenocarcinomas of colon were included. Apart from routine investigations preoperative evaluation was done with chest X-ray, contrast-enhanced computed tomography (CT) scan of abdomen and pelvis, colonoscopy and CEA (carcinoembryogenic antigen). PET-CT (positron emission tomography-computed tomography) was also included in workup and response assessment of some patients. Out of 105 patients, 61 (58%) patients had metastatic disease either synchronous or metachronous and those patients were taken up for analysis. Various treatment modalities used in this group of patients in our

setting were analyzed and correlated with progression-free survival (PFS) and OS.

Treatment protocols

Chemotherapy schedules

We have used different chemotherapy schedules for our metastatic colon cancer patients over this period of time as first-line therapy or alternative regimens.

1. Injection 5-FU and leucovorin
2. Injection 5-FU, leucovorin and oxaliplatin (FOLFOX)
3. Injection 5-FU, leucovorin and irinotecan (IFL)
4. Injection 5-FU, leucovorin and bevacizumab
5. Injection irinotecan and cetuximab
6. Oral capecitabine and leucovorin.

Resection

Surgical resection is, to date, the only potentially curative treatment of colorectal metastases.

The inclusion criteria for determining patient suitability for resection are as follows:

1. Up to three liver lesions,
2. Likelihood of achieving negative surgical margins while maintaining adequate liver reserve.

The presence of extrahepatic disease is generally considered a contraindication to hepatic resection, especially with peritoneal or abdominal lymphnode metastasis, where hepatic resection does not seem to improve survival at all.

Radiofrequency Ablation (RFA)

RFA is based on producing coagulative necrosis using a high-frequency alternating current that is delivered through an electrode placed in the center of the tumor.

Inclusion criteria for RFA are as follows:

1. Up to three liver lesions
2. Tumor size <3 cm
3. Patients who could not undergo resection due to comorbidity.

Hyperthermic intraperitoneal infusion

CRS and heated perioperative chemotherapy (HIPEC) were applied in our patients with isolated peritoneal metastasis. It demands a surgical procedure combined with cancer chemotherapy in the operating room. CRS involves five different peritonectomy procedures that are combined as needed with eight different visceral resections, in order to make patients with PM visibly disease-free. Immediately following the complete cancer resection and prior to intestinal reconstruction, the abdominal and pelvic spaces are flooded by a warm chemotherapy solution with injection cisplatin and 5-FU augmented by heat.

Endpoint and statistical analysis

The 2 year PFS and OS was the end point of our study. Since the overwhelming majority of recurrences happen within first 2 years, 2 year PFS is a reasonable surrogate for cure. Kaplan Meir survival curve was used for survival analysis. $P < 0.05$ was considered statistically significant. SPSS software version 18 was used for all statistical calculations.

RESULTS

Patient characteristics

Median age of presentation was 57 years ranging from 22 to 79 years. Out of 105 patients, 63 patients were males and 42 were females. Among tumors of the colon, sigmoid (41.9%) was the most common site of involvement followed by descending (29.5%), transverse (16.2%), and ascending colon (12.4%). A total of 58% of patients had metastatic disease either during presentation or developed subsequently during treatment or follow-up. A total of 21 patients presented with metastasis at presentation, whereas 40 patients developed metastasis metachronously. Liver was the most common site of metastasis (65.5%), followed by peritoneum (16.4%) and lung (13.1%). Most of the patient with hepatic metastasis presented with more than three lesions (55%), whereas solitary liver metastasis was seen in only seven patients [Table 1].

Treatment characteristics

Routine protocol was followed in nonmetastatic colon cancer patients. For liver metastasis, different modalities had been tried during this time period with evolution of newer advances in the field of oncology. Resection of liver metastasis was possible in six patients. RFA was done in six patients who were not fit for surgery and had 1 - 3 liver lesions. HIPEC was performed in 4 out of 10 patients who developed only peritoneal carcinomatosis. Novel-targeted agents like bevacizumab was used in four patients with

disseminated disease who were refractory to first line oxaliplatin-based chemotherapy. Anti-EGFR monoclonal antibody cetuximab was tried in four patients with wild-type k-ras. Regarding chemotherapy regimes, most of the patients received FOLFOX and 5-FU-leucovorin-based chemotherapy either as first-line or second-line treatment [Table 2].

Survival and outcome

With use of different modalities, it was possible to achieve 2-year PFS of around 28% [Figure 1] and a median OS of around 18 months [Figure 2].

Out of 13 patients who received bolus 5-FU-leucovorin alone, response (CR + PR) was seen in three patients (23.1%) with a median OS of 11 months. Response rate of around 45.5% (5/11) was seen in 11 patients who received FOLFOX-based chemotherapy alone. With addition of oxaliplatin-based chemotherapy median PFS of around 8 months could be achieved in our patients. Out of three patients who received IFL regime, one patient (33.3%) showed response with a median OS and PFS of 13 and 5.8 months, respectively.

Liver resection of colorectal metastases is associated with 3-year survival rate of 50% (3/6). After resection, recurrences are observed in four patients and involve the liver in 50% of the cases. For six patients who underwent RFA, 3-year survival rate of 50% (3/6) could be achieved. Out of four patients who underwent HIPEC, three of them achieved

Table 1: Patient characteristics

Patient Characteristics	No of patients(%)
Age (Median)	57 years
Sex	
Male	63 (60)
Female	42 (40)
Tumor Location	
Ascending	13 (12.4)
Transverse	17 (16.2)
Descending	31 (29.5)
Sigmoid	44 (41.9)
M-stage	
M0	44 (41.9)
M1	61 (58.1)
-Synchronous	21 (34.4)
-Metachronous	40 (65.6)
Site of metastasis	
Liver	40 (65.6)
Lung	8 (13.1)
Peritoneum	10 (16.4)
Others	3 (4.9)

Table 2: Treatment Modalities offered

No of patients	Chemo schedules	No of chemo cycles	Other procedures
13	5 FU+LV alone	Median 6	Nil
3	5 FU+LV 1 st line & FOLFOX 2 nd line+Capecitabine 3 rd line	Median 14	Nil
1	5 FU+LV	Median 6	Resection
1	5 FU+LV	Median 6	RFA
2	IFL 1 st line+Capecitabine 2 nd line	Median 8	Nil
2	FOLFOX -1 st line+IFL 2 nd line	Median 8	Nil
1	IFL alone	3	Nil
11	FOLFOX alone	Median 6	Nil
4	FOLFOX 1 st line+Bevacizumab 2 nd line	Median 11	Nil
5	FOLFOX	Median 6	RFA
5	FOLFOX	Median 6	Resection
4	FOLFOX 1 st line+Cetuximab 2 nd line	Median 9	Nil
2	5FU+LV 1 st line+FOLFOX2 nd line	12 (Mean)	HIPEC
2	FOLFOX	6 (Mean)	HIPEC
5	Capecitabine+LV alone	Median 6	Nil

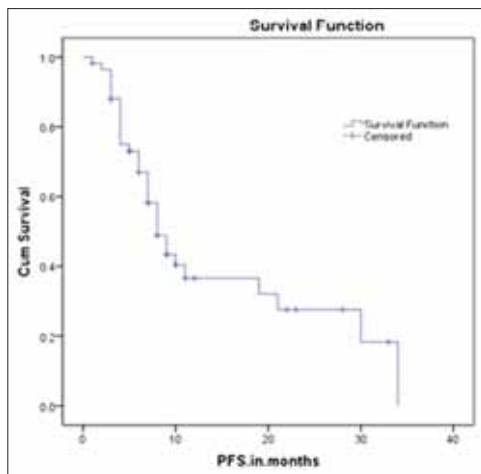


Figure 1: Kaplan-Meier survival curve showing progression-free survival

survival around 11 months, whereas one patient survived only 6 months. Out of four patients who received injection bevacizumab as second-line treatment in metastatic setting; one patient had partial response, two had stable disease, and another one progressed in spite of second-line therapy. The patient who achieved partial response had PFS of around 6 months and OS was around 1 year. One of four patients who received inj cetuximab in refractory setting showed partial response, one had stable disease and rest two had progressive disease. Mean OS of around 6 months was achieved in this group of patients.

DISCUSSION

CRC is the second most common cause of cancer death in developed countries and third most common malignancy worldwide. Nearly one fourth of patients have metastatic disease at diagnosis with a 5-year survival of less than 10% and a significant number of patients with loco regional disease go on to develop distant metastasis subsequently.

Treatment advances within the last decade have extended patient survival to the point, where metastatic colorectal cancer can be considered more of a chronic illness than an acutely fatal one. Oncologists now have a substantial number of options from which to select in designing a treatment strategy that looks beyond first-line therapy to multiple treatment phases.

The first real advance in first-line chemotherapy for patients with metastatic CRC came in late 1990s with the addition of active cytotoxic agents to a 5-FU/leucovorin base. The addition of irinotecan to bolus 5-FU/LV (IFL) increased median survival in patients with metastatic CRC from 12 to 14.8 months. Saltz *et al.*,^[11] showed that combining irinotecan with bolus 5-FU/LV resulted in a higher response rate, longer PFS, and longer OS in first-line metastatic CRC

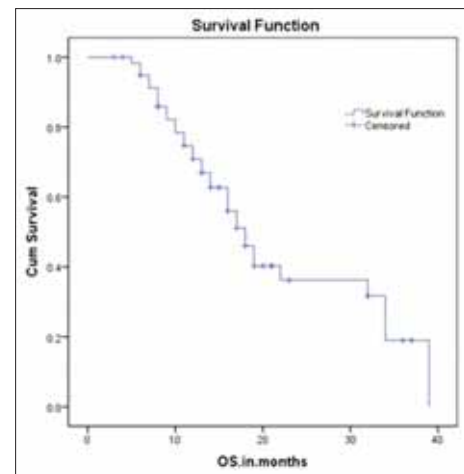


Figure 2: Kaplan-Meier survival curve showing overall survival

treatment. In this retrospective analysis, patients who received irinotecan-based chemotherapy showed response rate of 33% with a median OS of 14 months which is quite comparable with other studies. But at the same time, two out of three patients suffered from grade III diarrhea which had restricted us to use this kind of toxic regimen in large number of patients where performance status of the patients are poor.

Goldberg *et al.*,^[12] showed that FOLFOX produced a higher response rate (45%) and longer median survival time (19.5 months) than IFL. With the exception of peripheral neuropathy, the toxicity profile for FOLFOX also was more favorable than that of IFL. In this retrospective analysis, most of our patients received FOLFOX-based chemotherapy either as first-line or second-line agent. When FOLFOX used alone, it showed a response rate of (45.5%) with a PFS of 8 months. They had achieved a median OS of around 18 months which is not inferior to Western studies.

VEGF is a specific mitogen for the endothelial cell and one of the most potent proangiogenic factors. It appears to be a particularly attractive target for CRC. Phases II and III studies have evaluated the addition of bevacizumab to 5-FU/LV as a standard option for the first-line treatment of metastatic CRC. Giantonio *et al.*,^[13] showed the addition of bevacizumab to the FOLFOX chemotherapy regimen, provides a statistically significant and clinically meaningful improvement in OS, compared to FOLFOX alone, in patients with advanced or metastatic disease in whom the disease has progressed after adjuvant chemotherapy with FOLFIRI. In this retrospective analysis, bevacizumab was added with 5-FU/LV in four patients who were refractory to FOLFOX-based chemotherapy. One of those four patients responded partially (25%) to bevacizumab and mean OS was 12.1 months which could be matched to other studies.

The EGFR signaling is thought to play a pivotal role in tumor growth and progression of CRC. Cetuximab has

been studied both a single agent and in combination with irinotecan for patients with disease progression on initial therapy for metastatic disease. Cunningham *et al.*,^[14] evaluated the response of cetuximab alone and cetuximab plus irinotecan in patients with irinotecan refractory CRC. The response rates were 10.8% for cetuximab alone and 22.9% for cetuximab plus irinotecan. In this retrospective analysis, one out of four patients (25%) showed partial response with a mean OS of 6.2 months.

Resection offers the greatest likelihood of cure for patients with liver-isolated CRC. In surgical case series, 5-year survival rates after resection range from 31 to 58%, averaging 40%, and surgical mortality rates are generally <5%.^[15,16] Because of its clear survival impact, surgical resection is the treatment of choice when feasible. Unfortunately, no more than 20% of the patients with isolated hepatic metastasis are amenable to potentially curative resection. Most are nonsurgical candidates because of tumor size, location, multifocality, or inadequate hepatic reserve. In this retrospective analysis, 15% (6/40) of the patients with liver metastasis underwent surgical resection and among them three patients (50%) achieved 3-year OS.

As many as 90% of patients with metastatic CRC are not candidates for surgical treatment.^[17] Criteria for unresectable metastases include bilobar disease that cannot be completely excised, proximity to major vasculature structures precluding margin-negative resection, and comorbid conditions that preclude surgery. For these untreated patients, survival is less than at 5 years.^[18] This emphasizes the need for alternative forms of disease management. RFA has emerged as a viable option for many patients who are not surgical candidates. Solbiati *et al.*,^[19] reported an overall median survival of 36 months in 117 patients but for those with metastasis below 2.5 cm in diameter the median survival increased to 42 months. In a study by Gillam and Lees, they have reported 5-year survival of 34% from the diagnosis of liver metastasis but for those with no more than three tumors below 3.5 cm in diameter, the 5-year survival from the diagnosis of liver metastasis increased to 40%. In this retrospective analysis, patients with up to three liver lesions, size <3 cm but not amenable to surgical resection were taken up for RFA and 3-year survival rate of around 50% could be achieved.^[20]

Peritoneal metastases are a common presentation for patients with metastatic CRC, and the median survival of patients with peritoneal metastasis is approximately 1 year. In a majority of patients, the disease remains limited to the peritoneal cavity. Therefore, investigators have applied CRS and heated peritoneal chemotherapy as a standard approach for selected patients with peritoneal metastasis from CRC. Sugarbaker and Jablonski^[21] showed 3-year survival of 35%

in 51 patients with peritoneal metastasis from colon cancer treated with CRS plus intraperitoneal 5-FU and mitomycin C. In 2003, Verwaal from Amsterdam showed a 3-year projected survival of 38% in 54 patients treated by CRS and hyperthermic intraperitoneal mitomycin C with adjuvant systemic 5-FU.^[22] In this retrospective analysis, 75% (3/4) of patients who underwent HIPEC survived around 11 months and a 3-year survival of 25% (1/4) was seen.

With use of various modalities of treatment in these heterogeneous group of patients, we are able to achieve median OS of 18 months and 2-year PFS of 28% which is not at all inferior, especially in a developing country like ours, where most of the patients present with poor general condition.

CONCLUSION

It's a long journey since 1958 from an era of 5-FU alone to a recent era of resection, RFA, oxaliplatin, irinotecan-based chemo or magic bullets like bevacizumab or cetuximab. Advancement of treatment of metastatic CRC in those last 50 years has extended the survival to such an extent that it can be considered as a chronic disease rather than an acutely fatal entity. This retrospective analysis also showed that metastatic colon cancer can be converted into a chronic disease with enhancement of 2-year PFS up to 28% and median OS of around 18 months with availability of plethora of new drugs, biological agents, surgery, and modern techniques like RFA or HIPEC. Maximizing efficacy must be balanced with minimizing toxicities, particularly in patients with active disease. Furthermore, because adjuvant and first-line therapy can influence subsequent treatment selection, various scenarios along a treatment continuum must be considered from the outset to ensure that each patient has the best chance of receiving—and benefiting from—all available therapies. Because there are no prospective data to determine with precision which patients might benefit from which regimens and sequences at present, therapy should be individualized based on known clinical factors. Prospective clinical trials as well as retrospective analyses of existing clinical databases will provide more definitive guidance.

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