



# Curative treatment for metastatic colorectal cancer in the young population: is it worth it?

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**Background:** A significant proportion of patients with colorectal cancer (CRC) presents with metastatic disease. In younger patients, a more aggressive approach is often adopted in an attempt to achieve cure and improve survival. The aim of this paper is to review the management and outcomes of young patients with metastatic CRC.

**Methods:** All patients under 50 years diagnosed with CRC in a single institution from January 2007 to December 2015 were reviewed. Patient demographics, details of their treatments, progress and outcomes of treatment were collected for our review.

**Results:** There were 154 newly diagnosed CRC patients who were <50 years old during the study period. Thirty-three patients (21.4%) had stage IV disease on presentation. Seventeen (51.5%) of these 33 patients were treated with curative intent; 9 (52.9%) of whom underwent upfront surgical resection alone while the remaining 8 (47.1%) patients had neoadjuvant therapy followed by surgical resection. Among the 16 patients who were treated with palliative intent, 9 (56.3%) had surgery while 7 (43.7%) had definitive chemo- or radio-therapy. There was no significant difference in the median survival of patients treated with curative and palliative intent (29 vs. 24 months, P=0.140).

**Conclusions:** Young CRC patients with stage IV disease typically survive for 2 years upon diagnosis. Those who were treated and underwent surgery with curative intent have a slightly longer but not statistically significant median survival than those treated with palliative intent. The role of aggressive treatment in these young patients with metastatic patients merits further evaluation.

**Keywords:** Colorectal neoplasms; neoplasm metastasis; young colorectal cancer; prognosis; surgery; quality of life

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## Introduction

Colorectal cancer (CRC) is the commonest cancer in Singapore and accounts for significant morbidity and mortality (1). A significant proportion of patients with CRC present prior to 50 years old and these individuals often represent the most economically productive population in any society (2-5). Of those who developed CRC when

they are young, a significant proportion of them often also present with advanced disease (2-5) with more than 20% of them having metastatic disease on diagnosis (6,7).

There has been growing interest in the management of metastatic CRC in recent years, and the boundaries of curative surgery in this group of patients continue to be redefined. Young patients with metastatic CRC are often treated aggressively to provide them with the best chance of

cure. Although these younger patients are often medically healthy and have greater functional reserves, surgery and its accompanying systemic or local treatment are not without its implications. These risks should only be justified if there are truly significant improvements in survival and quality of life, with an acceptable rate of recurrence.

The aim of this study is to review the management and outcomes of young patients with CRC who presented with metastatic disease. Whilst pursuing curative treatment appears promising and instinctive, physicians ought to give patients and families realistic expectations of treatment outcomes, and also consider the psychosocial and financial burdens that patients and family face when counselling them on the treatment options.

## Methods

A retrospective review of all patients, who were under the age of 50 years, diagnosed with metastatic CRC in a single institution from January 2007 to December 2015 was conducted. These patients were identified from a pre-existing prospectively maintained colorectal cancer database. Confirmation of the malignancy was achieved histologically while staging was performed with computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) or a combination of the above.

The management of each patient was discussed at a multi-disciplinary tumor board, consisting of a team of medical oncologist, radiation oncologists, surgeons and radiologists. All patients who underwent curative surgery subsequently had adjuvant chemotherapy.

Data collected included demographics, clinical presentations, disease characteristics, treatment received and outcomes. Results were analyzed with SPSS version 21.0 and  $P < 0.05$  was considered statistically significant. Univariate analysis was performed using Mann-Whitney U test for continuous variables and Pearson's Chi square or Fisher's Exact test for categorical variables. Cumulative overall survival rate was calculated by the Kaplan-Meier method and compared by the log-rank test. The study was approved by the National Healthcare Group's Domain Specific Research Board, reference number 2015/00842.

## Results

From January 2007 to December 2015, a total of 1,367 patients were diagnosed with CRC in our institution, of

which 154 patients (11.3%) were under the age of 50, of which 33 (21.4%) had stage IV disease.

The median age at diagnosis for the study group was 45 years (range, 19–49 years). Majority of the patients ( $n=23$ , 69.7%) first presented to the emergency department (ED). Amongst them, 11 patients (47.8%) presented with intestinal obstruction or perforation from the cancer. *Table 1* provides further details on the demographics and clinical presentations of our study population.

The majority of the patients ( $n=28$ , 84.8%) had left sided cancers. Nine patients (27.3%) had more than 1 site of metastasis. Information on tumor location and histopathologic variables are found in *Table 1*.

Twenty-five (75.8%) patients underwent surgery, of which 17 (68%) were with curative intent. Of the 17 patients (51.5%) who were treated with curative intent, 9 (52.9%) patients underwent upfront surgical resection followed by adjuvant treatment, 6 (35.3%) patients had a trial of neoadjuvant therapy prior to surgical resection and 2 (11.8%) patients had successful endoscopic stents followed by a trial of neoadjuvant treatment. Among the 16 (48.5%) patients treated with palliative intent, 9 (56.3%) patients underwent surgery to either have their tumour resected or creation of a diverting stoma. *Table 2* illustrates the treatment details of our study population.

Among the 25 patients who underwent surgery, the median length of hospitalisation was 8 days (range, 6–23 days). None of them experienced a surgical morbidity of Clavien III and above. Patients were followed up for a median duration of 14.0 months (range, 1.0–51.0 months).

Among the 17 patients treated with curative intent, 8 (47.1%) had disease recurrence, majority were distant recurrences, with a median time to recurrence of 6.5 months (range, 1.0–24.0 months). There were 14 (42.4%) CRC-related mortalities in our study population, and the median time to death from diagnosis was 18.0 months (range, 3.0–50.0 months). There was no significant difference in median survival between the patients who underwent curative treatment and those who had palliation (29 vs. 24 months,  $P=0.140$ ) as illustrated in *Table 3* as well as in the Kaplan-Meier survival curve in *Figure 1*. The outcomes of our study population are shown in *Table 2*.

## Discussion

The overall incidence of CRC in the general population has declined in recent years, and this is largely attributed to the increase in proportion of population undergoing screening

**Table 1** Demographics and tumour characteristics

Variable	n=33 (% or range)
Median age at diagnosis, years	45.0 (19.0–49.0)
Gender	
Male	15 (45.5)
Female	18 (54.5)
Site of presentation	
Emergency department	23 (69.7)
Specialist outpatient clinic	10 (30.3)
Presentation with tumor crisis	
Intestinal obstruction	8 (24.2)
Perforation	3 (9.1)
Other presenting symptoms	
Abdominal pain	24 (72.7)
Change in bowel habits	18 (54.5)
Constitutional symptoms	15 (45.5)
Loss of weight	14 (42.4)
Per rectal bleeding	13 (39.4)
Constipation	12 (36.4)
Abdominal distension	11 (33.3)
Diarrhoea	9 (27.3)
Symptomatic anemia	5 (15.2)
Decrease in stool caliber	3 (9.1)
Metastatic symptoms	3 (9.1)
Tenesmus	2 (6.1)
Tumor site	
Rectum	10 (30.3)
Sigmoid colon	9 (27.3)
Rectosigmoid	6 (18.2)
Transverse colon	2 (6.1)
Splenic flexure	2 (6.1)
Descending colon	1 (3.0)
Ascending colon	1 (3.0)
Hepatic flexure	1 (3.0)
Cecum	1 (3.0)

**Table 1** (continued)**Table 1** (continued)

Variable	n=33 (% or range)
Sites of metastasis	
Liver	21 (63.6)
Peritoneum	11 (33.3)
Lung	9 (27.3)
Gynaecological	6 (18.2)
Small/large bowel	1 (3.0)
Histological grade	
Well differentiated	0 (0.0)
Moderately differentiated	24 (72.7)
Poorly differentiated	9 (27.2)
Lymphovascular invasion	18 (54.5)
Perineural invasion	19 (57.6)

and the removal of pre-malignant lesions (8,9). However, the incidence of CRC in the population younger than 50 years old appears to be increasing (2-5,8). A possible explanation is the rise in incidence of CRC risk factors among the young, such as metabolic syndromes like diabetes mellitus and obesity (9,10). Although there is increasing data on the clinical presentations, disease characteristics and outcomes of young CRC patients (2-5,11-16), there remains a scarcity of information on the subgroup of patients with metastatic disease.

Once believed to be a terminal disease with a dismal overall survival (17), metastatic CRC is now potentially curable in a select group of patients, achieving 5-year survival rates of up to 45% (18). Various studies have reported survival and quality of life benefits in patients with metastatic CRC who undergo curative surgery (18-22). Younger patients, whom are associated with more advanced and aggressive diseases do possess better oncological outcomes than their older counterparts (23). This is observed even amongst patients with metastatic disease (23-27). This may thus support the push for aggressive potentially curative treatment in the younger age group.

There are several important observations from our study. Firstly, patients who undergo treatment with a palliative intent do have a reasonable median survival of 2 years. The

**Table 2** Treatment and outcomes

Variables	n=33 (% or range)
Underwent surgery	
Yes	25 (75.8)
No	8 (24.2)
Primary tumor resected	
Yes	21 (63.6)
No <sup>†</sup>	12 (36.4)
Curative intent—initial treatment	17 (51.5)
Upfront surgical resection	9 (52.9)
Neoadjuvant therapy <sup>†</sup>	6 (35.3)
Endoscopic stenting followed by neoadjuvant therapy	2 (11.8)
Palliative intent—treatment	16 (48.5)
Surgery	9 (56.3)
Tumor resection	5 (31.3)
Diverting stoma	4 (25.0)
Chemo/radio-therapy only	7 (43.7)
Operative urgency (n=25)	
Emergency	9 (36.0)
Elective	16 (64.0)
Resection description (n=21)	
Anterior resection	13 (61.9)
Subtotal/ total colectomy	1 (4.8)
Right hemicolectomy	3 (14.3)
Extended right hemicolectomy	3 (14.3)
Left hemicolectomy	1 (4.8)
Length of stay for surgery (days)	8 (6.0–23.0)
Surgical complications (n=25)	
Post-op complications	3 (12.0)
Clavien grade I	2 (66.6)
Clavien grade II	1 (33.3)
None	22 (88.0)
Type of complication	
Wound infection	1 (3.0)
Intra-abdominal abscess	1 (3.0)
Pneumonia	1 (3.0)

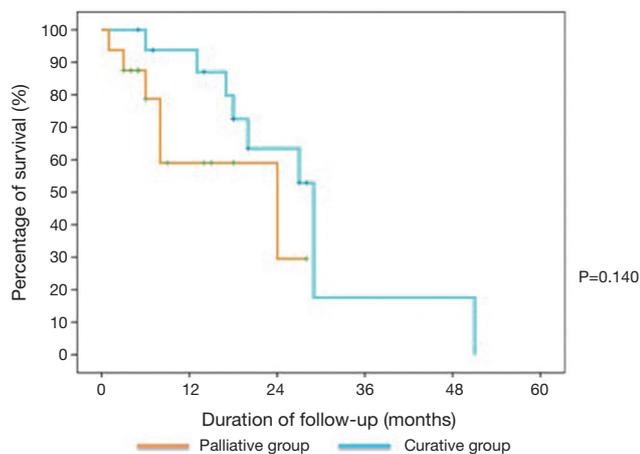
**Table 2** (continued)**Table 2** (continued)

Variables	n=33 (% or range)
Median follow-up (months)	14.0 (1.0–51.0)
Recurrence (patients treated with curative intent; n=17)	
Yes	8 (47.1)
Local	1 (12.5)
Distant	6 (75.0)
Local and distant	1 (12.5)
Sites of distant recurrence	
Liver	7 (100.0)
Lung	4 (57.1)
Peritoneal	2 (28.8)
Pelvic	1 (14.3)
No	8 (47.1)
NA (unfit for PTR after neoadjuvant)	1 (5.8)
Interval to recurrence (months) (n=8)	6.5 (1.0–24.0)
Outcomes of patient with recurrences	
Dead	7 (87.5)
Alive	1 (12.5)
Death interval from recurrence (months)	11.0 (4.0–44.0)
Death	
Yes	15 (45.5)
CRC related	14 (42.4)
Non-CRC related	1 (3.1)
No	18 (54.5)
Death interval (months) (n=12)	18.0 (3.0–50.0)

<sup>†</sup>, 1 patient had disease progression after initial neoadjuvant chemotherapy and hepatic metastasectomy and was unsuitable for curative resection of primary tumor. NA, not available; CRC, colorectal cancer; PTR, primary tumour resection.

**Table 3** Survival of curative vs. palliative group

Variable	Curative, n=17	Palliative, n=16	P value
Survival	29.0 (23.1–34.9)	24.0 (0.5–47.5)	0.140



**Figure 1** Kaplan-Meier curves comparing survival of curative vs. palliative groups.

advent of newer chemotherapeutic and immunological agents would have accounted for this improved survival over the years. In these individuals with extensive and unresectable systemic disease, the intention of primary resection of the tumour could be reserved for alleviation of symptoms and prevention or life-saving treatment of tumor crisis such as obstruction, perforation or bleeding. It was perhaps fortunate that none of our patients who underwent surgery had any significant morbidity. This could be because patients in this age group are often healthy and have greater functional reserves

In addition, the median survival of patients who underwent treatment with curative intent, including surgery, was nearly 30 months in our study. Perhaps one could downplay the significance of a 5-month improvement in overall survival that is conferred by curative treatment, but these 5 months could be extremely important to these individuals, especially in those who have yet come to acceptance and needs the time to make plans for those they are leaving behind upon demise. That said, whether the associated morbidities and impediments to their quality of life from the repeated surgeries (to the primary and the systematic disease) and perhaps carrying a stoma were worthy of these 5 months merits further evaluation.

Over treatment is a genuine concern in the management of these young mCRC patients. Oncologists and surgeons tend to be far more aggressive in the management of these younger adults, and often attempt to deplete the arsenal of treatment options before giving in to palliative care. This

is likely because these adults are in the most economically productive phase of their lives and have great potential in the years ahead, and the attending surgeons and oncologists often become emotionally attached to these patients. Costly treatments, including the use of immunological therapy may only marginally improve survival but places huge financial and psychosocial burdens on the patient and family. It may be worthwhile to explore palliative options early instead of attempting to exhaust all available treatment options with no intent of closure or accepting the inevitable demise of these patients.

Although attempting and pushing for curative treatment is often the instinctive choice in the management of young patients with metastatic CRC, and though it may truly render half of these patients disease free, it is imperative to remember that the barrage of treatments will fail in the other half of these patients and at the same time place a significant emotional and financial burden on the patient and family. It is therefore the responsibility of the attending physician to spend the time and effort to counsel these patients and their families extensively to ensure that goals of therapy are clearly defined and achievable.

The various limitations of our study include it being a retrospective study with its own inherent biases. The small sample size and short duration of follow-up may also limit the validity of our study. However, young patients who present with metastatic CRC are uncommon and it is difficult to conduct large-scale studies for this group of patients. Although this is a highly selected group of patients, they represent an important population that should not be neglected. It is thus important to conduct future prospective studies with the aim of better selecting patients who will benefit the most from treatment with curative intent.

## Conclusions

Young CRC patients with stage IV disease typically survive for 2 years upon diagnosis. Those who were treated with curative intent have a slightly longer and not statistically significant median survival than those treated with palliative intent. The role of aggressive treatment in these young patients with metastatic patients merits further evaluation.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by the National Healthcare Group's Domain Specific Research Board, reference number 2015/00842.

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