

# The Prognostic and Curative Benefits of Primary Tumor Resection versus No Resection in Stage IV Colorectal Cancer: A Comparative Study

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## Abstract

**Background:** Colorectal cancer (CRC) who is initially diagnosed with single or multiple synchronous distant metastases has an incidence of about 20% of all CRC patients. There is a controversy regarding the role of resection of the primary tumors in those patients. The aim of this study was to explore the prognostic roles and survival advantages of surgical excision of the primary colonic tumor in patients with CRC who are primarily diagnosed with distant metastases. **Patients and Methods:** We included forty patients who were diagnosed initially with stage IV CRC. We have divided the included patients into two categories the first one included 20 patients that underwent surgical excision of the primary cancer followed by administration of chemotherapy and the remaining 20 patients were initially given chemotherapy without excision of the cancer. We followed patients for 24 months to detect progression, response to chemotherapy, recurrence free survival and overall survival rates. **Results:** There is statistically significant difference between patients underwent different initial management techniques regarding N stage of the tumor ( $p = 0.039$ ), response to chemotherapy ( $p = 0.048$ ), occurrence of relapse ( $p = 0.022$ ), disease free survival (DFS) ( $p = 0.027$ ) or overall survival (OS) rates ( $p = 0.001$ ) (DFS and OS were significantly higher among patients who received initial surgical management. Primary surgical removal of the tumor improved OS rate by 8 months ( $p = 0.001$ )). **Conclusion:** Surgical removal of the primary malignancy in mCRC patients before chemotherapy

administration improves patients' survival rates and response to chemotherapy that lead to a better prognosis.

## Keywords

Metastatic CRC (mCRC), Surgical Resection, Chemotherapy, Survival

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## 1. Introduction

Colorectal cancer (CRC) ranks as the 3rd and 2nd most commonly diagnosed malignancy in males and females, respectively [1] [2]. There is a marked improvement in diagnostic modalities and medical screening programs which lead to early diagnosis of CRC in early stages, however about twenty percent of CRC are initially diagnosed at late stages with distant metastasis and have a poor prognosis [3] [4]. There is a controversy regarding the role of excision of the primary cancer in those patients. Primary resection may be a good palliative treatment strategy for those patients with severe local symptoms as obstruction, bleeding or perforation. Surgical removal of the primary cancer might be also performed as a curative modality in some patients.

Additionally, as there is marked advancement of chemotherapeutic agents, starting chemotherapeutic regimens without surgical removal of the primary tumor was found to have some promising results in mCRC patients [5]. So, making adequate surgical or medical therapeutic plan for mCRC patients is a must, putting in consideration; primary site of the tumor, site and number metastases, local and systemic symptoms, comorbidities and performance status of the patients. As some patients were found to develop recurrence after curative surgical resection of the primary tumor which leads to extremely poor prognosis while others were not and surgery was improving their prognosis [6].

**The aim of this study was to** explore the prognostic roles and survival advantages of surgical excision of the primary colonic tumor in patients with CRC who are primarily diagnosed with distant metastases.

## 2. Patients and Methods

This is a prospective study performed in General Surgery Department, Zagazig University Hospitals in the period from March 2017 to May 2019 where we included forty patients who were diagnosed initially with stage IV CRC. All patients underwent colonoscopy assessment in Internal Medicine Department, Faculty of Medicine, Zagazig University for confirmation of diagnosis, resectability and preoperative evaluation. We have divided the included patients into two categories the first one included 20 patients that underwent surgical excision of the primary cancer followed by administration of chemotherapy and the remaining 20 patients were initially given chemotherapy without excision of the cancer. We followed patients for 24 months to detect progression, response to chemotherapy, recurrence free survival and overall survival rates.

## 2.1. Inclusion Criteria of Patients Who Have Undergone Surgery

- Histologically confirmed CRC with synchronous metastases which are not liable to curative therapy;
- Resectable primary tumor;
- Patient was found to be able to tolerate surgery;
- Age of patients is  $\geq 18$  years;
- A written informed consent was taken from all patients.

## 2.2. Exclusion Criteria

- Cancers arising from the anal canal;
- Neuroendocrine carcinoma and gastrointestinal stromal tumors;
- Local severe tumor-associated symptoms requiring urgent surgery as severe bleeding which require blood transfusion, intestinal obstruction, perforation or severe resistant pain at the primary tumor site;
- Patients cannot afford surgery;
- Extensive peritoneal spread;
- Preoperative chemo- or radiotherapy in the last six months before surgery;
- Expected absence of patients' compliance.

Surgical resection of the tumor in addition to lymphadenectomy was performed according to the CRC surgical management guidelines mentioned by the CRC Japanese Society [7].

We recorded patients' clinicopathological criteria as age, sex of the patients, site, size, grade of the tumor and depth of its invasion. Regarding the site of the primary tumor, we described tumors which are arising from the cecum, ascending colon and transverse colon (up to the splenic flexure), have been named right-sided cancer and underwent surgical right hemi-colectomy, while those which arise from beginning of descending colon to rectum have been named left-sided cancer and underwent surgical left hemi-colectomy. CRC were pathologically classified based on the 7th edition Union for International Cancer Control (UICC) criteria, seventh edition in Pathology Department, Faculty of Medicine, Zagazig University [8].

For the 20 patients who have taken chemotherapy after surgical excision of the primary tumor and for the other 20 patients who initially started chemotherapy without surgery, the regimens were conformed according to Japanese guidelines as FOLFIRI, FOLFOX or CAPEOX [8]. We followed our patients for 2 years by regular physical examination, laboratory evaluation CA 19-9 and CEA every three months. We performed abdominal computed tomography (CT) every 4 - 6 months.

## 3. Results

### 3.1. Patient Characteristics

The detailed pathological and clinical data of the patients are shown in **Table 1**.

We included 28 (70%) male patients and 12 (30%) female patients their age

**Table 1.** Comparison between the studied surgical techniques regarding demographic, pathological, operative, postoperative data and tumor markers.

Variables	Total N = 40 (%)	Initial Management Techniques		Test	
		Surgery First N = 20 (%)	Chemotherapy First N = 20 (%)	$\chi^2/t$	p
<b>Age (years):</b>					
Mean $\pm$ SD	56.78 $\pm$ 12.14	56.3 $\pm$ 12.18	57.25 $\pm$ 12.41	-0.244 <sup>y</sup>	0.808
Range	29 - 80	30 - 75	29 - 80		
<b>Gender:</b>					
Male	28 (70)	14 (50)	14 (50)	0 <sup>o</sup>	1
Female	12 (30)	6 (50)	6 (50)		
<b>Size of the tumor (cm):</b>					
<5 cm	13 (32.5)	5 (38.5)	8 (61.5)	1.026 <sup>oo</sup>	0.311
$\geq$ 5 - 10 cm	27 (67.5)	15 (55.6)	12 (44.4)		
<b>Histopathological type:</b>					
Conventiosional adenocarcinoma	28 (70)	15 (53.6)	13 (46.4)	0.476 <sup>oo</sup>	0.49
Mucoid carcinoma	12 (30)	5 (41.7)	7 (58.3)		
<b>Initial site:</b>					
Ascending colon	9 (22.5)	4 (44.4)	5 (55.6)	1.854 <sup>oo</sup>	0.603
Rectosigmoid	9 (22.5)	3 (33.3)	6 (66.7)		
Descending colon	15 (37.5)	9 (60)	6 (66.7)		
Transverse colon	7 (17.5)	4 (57.1)	3 (42.9)		
<b>Grade:</b>					
I	6 (15)	3 (50)	3 (50)	1.047 <sup>oo</sup>	0.585
II	15 (37.5)	9 (60)	6 (40)		
III	19 (47.5)	8 (42.1)	11 (57.9)		
<b>T stage:</b>					
T2	4 (10)	2 (50)	2 (50)	0.181 <sup>oo</sup>	0.979
T3	9 (22.5)	4 (44.4)	5 (55.6)		
T4a	13 (32.5)	7 (53.8)	6 (46.2)		
T4b	14 (35)	7 (50)	7 (50)		
<b>N stage:</b>					
N1	7 (17.5)	5 (71.4)	2 (28.6)	6.468 <sup>oo</sup>	0.039*
N2	11 (27.5)	8 (72.7)	3 (27.3)		
N3	22 (55)	7 (31.8)	15 (68.2)		
<b>M stage:</b>					
M1a	16 (40)	11 (68.8)	5 (31.2)	3.75 <sup>oo</sup>	0.043
M1b	24 (60)	9 (37.5)	15 (62.5)		
<b>TNM stage:</b>					
Iva	16 (40)	11 (68.8)	5 (31.2)	3.75 <sup>oo</sup>	0.049
Ivb	24 (60)	9 (37.5)	15 (62.5)		
<b>Site of distant metastasis:</b>					
Liver	16 (40)	11 (68.8)	5 (31.2)	5.628 <sup>oo</sup>	0.06
Liver + peritoneum	9 (22.5)	5 (55.6)	4 (44.4)		
Liver + lung	15 (37.5)	4 (26.7)	11 (73.3)		
<b>CA 19-9:</b>					
Positive	17 (42.5)	6 (35.3)	11 (64.7)	4.561 <sup>oo</sup>	0.102
Negative	12 (30)	9 (75)	3 (25)		
Non applicable	11 (27.5)	5 (45.5)	6 (54.5)		
<b>CEA:</b>					
Positive	15 (37.5)	5 (33.3)	10 (66.7)	4.744 <sup>oo</sup>	0.093
Negative	12 (30)	9 (75)	3 (25)		
Non applicable	13 (32.5)	6 (46.2)	7 (53.8)		

<sup>o</sup>Chi square test, <sup>y</sup>Independent sample t test.

ranged from 29 - 80 years old and mean age =  $56.78 \pm 12.14$ .

### 3.2. Clinicopathological Results (Table 1, Figures 1-2)

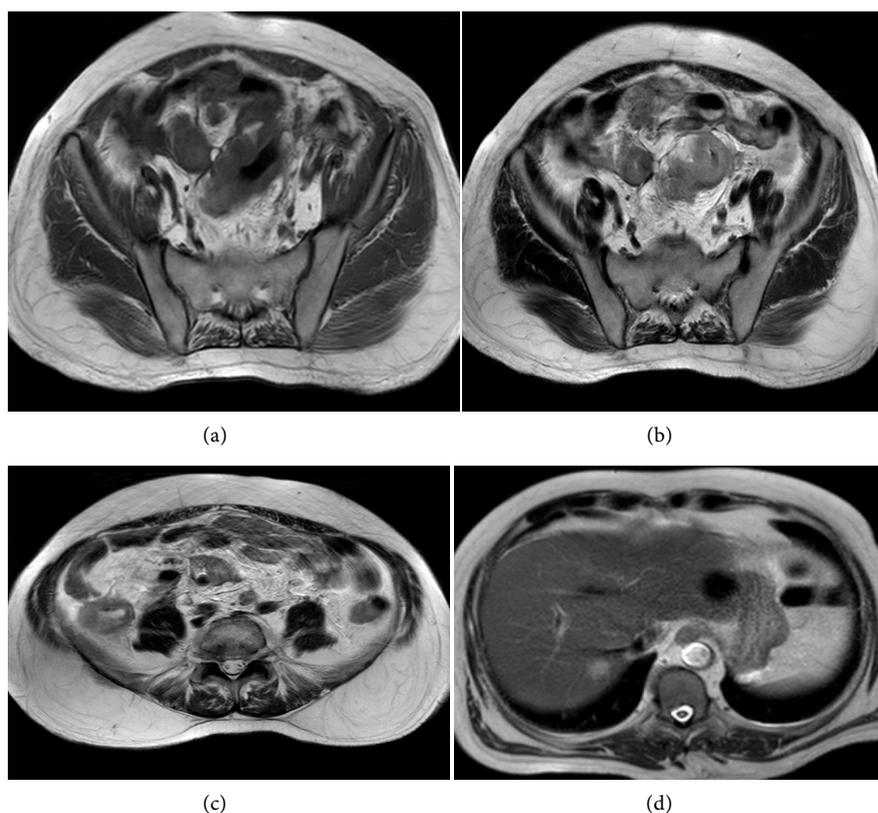
There is a statistically non-significant difference among patients who underwent different initial management techniques regarding age or gender of the patients, site, size, grade and CA 19-9 and CEA levels, site of distant metastases.

There is a statistically significant difference among patients who underwent different initial management techniques regarding N stage of the tumor (the largest percentage of patients received initial chemotherapy had N3 stage) ( $p = 0.039$ ).

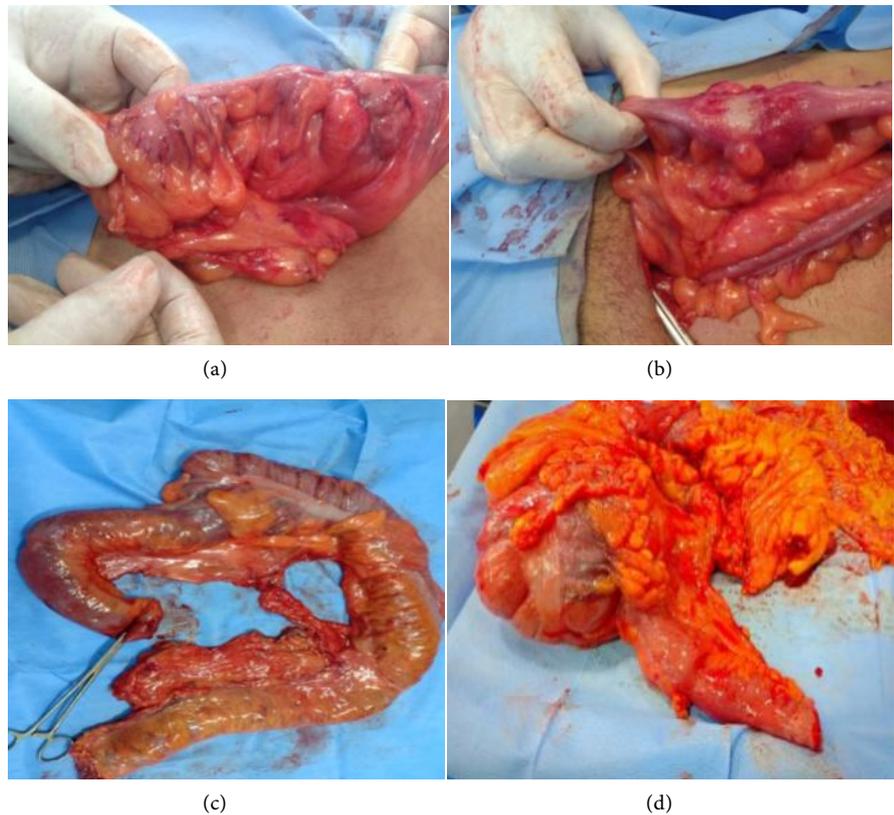
### 3.3. Prognosis, Follow-Up and Survival Results (Tables 2-3, Figure 3)

Regarding the prognosis, the median follow-up period of included patients was 11.4 months, and the 2-year overall survival (OS) was 19.1%.

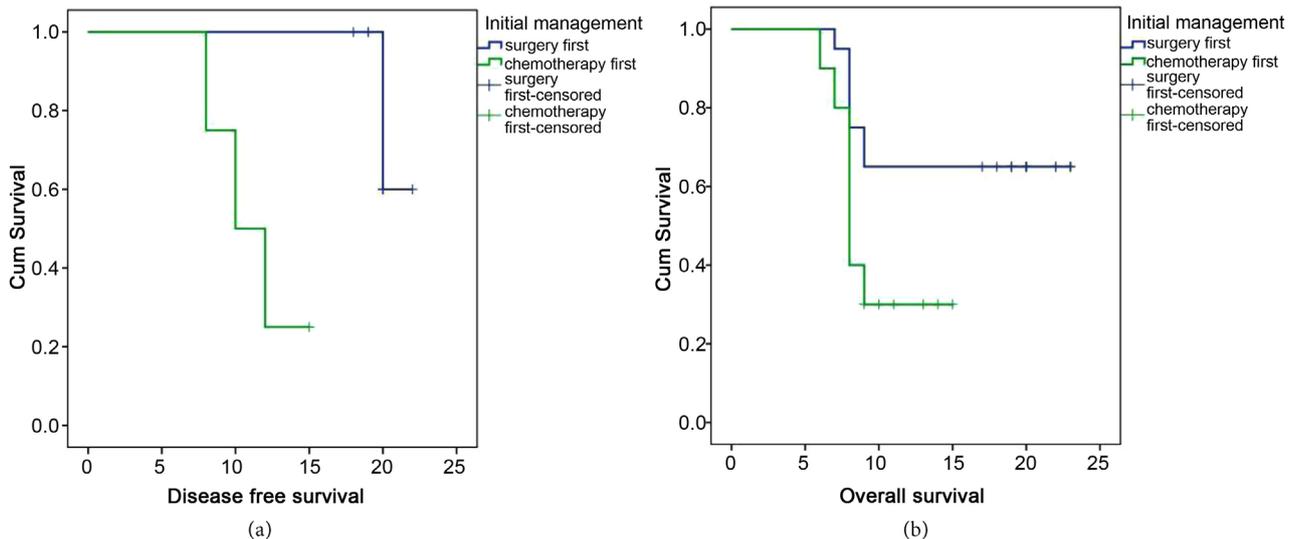
Mean DFS in the group that we started with surgery first was 21.2 while median DFS in the group that we started with chemotherapy first was 11.25 with a significant difference between them. Mean OS in the group that we started with



**Figure 1.** Metastatic colon cancer, colonic mass on colonoscopy. (a) axial T1WI, (b) axial T2WI show extensive diffuse circumferential mucosal wall thickening affecting the entire length of the sigmoid colon causing significant narrowing of its lumen, there is speculation of the outer margin of the lesion exerting desmoplastic reaction into the adjacent fat, the lesion display low signal intensity on T1WI (a) & high on T2WI (b). (c) and (d) axial T2WI show enlarged Lt iliac lymph node (c), two hepatic focal deposits (d).



**Figure 2.** Intra and post-operative appearance of different types of surgical resection of colorectal cancer (CRC) with metastases (a) adeno-carcinoma of the transverse colon (b) adeno-carcinoma of the sigmoid colon ((c) and (d) Right hemi-colectomy for adeno-carcinoma of the ascending colon.



**Figure 3.** (a) Kaplan Meier plot showing disease free survival among mCRC patients underwent different management techniques. (b) Kaplan Meier plot showing overall survival among mCRC patients underwent different management techniques.

surgery first was 17.8 while mean OS in the group that we started with chemotherapy first 9.9, with a significant difference between them.

**Table 2.** Comparison between the studied surgical techniques regarding response to treatment and patient outcome (relapse and death).

Variables	Initial Management Techniques			Test	
	Total	Surgery First	Chemotherapy First	$\chi^2/Z$	p
	N = 40 (%)	N = 20 (%)	N = 20 (%)		
<b>Response to treatment:</b>					
PD	13 (32.5)	5 (38.5)	8 (61.5)	2.186 <sup>∞</sup>	0.048
SD	7 (17.5)	3 (42.9)	4 (57.1)		
PR	8 (20)	4 (50)	4 (50)		
CR	12 (30)	8 (66.7)	4 (33.3)		
<b>Relapse (n = 12):</b>					
Absent	7 (58.3)	6 (85.7)	1 (14.3)	Fisher	0.022
Present	5 (41.7)	2 (40)	3 (60)		
<b>Death</b>					
No	19 (47.5)	13 (68.4)	6 (31.6)	4.912	0.027*
Yes	21 (52.5)	7 (33.3)	14 (66.7)		
<b>Disease free survival:</b>					
Median	7	16.5	7	-2.21 <sup>‡</sup>	0.027*
Range	4 - 22	4 - 22	5 - 15		
<b>Overall survival:</b>					
Median	9	19	8	-3.352 <sup>‡</sup>	0.001**
Range	6 - 23	7 - 23	6 - 15		

\*p < 0.05 is statistically significant, \*\*p ≤ 0.001 is statistically highly significant, <sup>‡</sup>Mann Whitney test, <sup>∞</sup>Chi square test.

**Table 3.** Comparison between the studied groups regarding disease free survival and overall survival.

Time	Initial Management Techniques				Mantel Cox Test
	Surgery First		Chemotherapy First		p
	Mean	SEM	Mean	SEM	
DFS	21.2	0.44	11.25	1.29	0.004*
OS	17.8	1.59	9.9	0.77	0.019*

\*p < 0.05 is statistically significant.

There is a statistically significant difference among patients who underwent different initial management techniques regarding response to treatment (p = 0.048) occurrence of relapse (p = 0.022), disease free survival (DFS) (p = 0.027) or overall survival (OS) rates (p = 0.001) (DFS and OS were significantly higher among patients who received initial surgical management. Two thirds of patients who died by the end had treated initially by chemotherapy. Primary surgical resection of the tumor improved OS rate by 8 months (p = 0.001).

#### 4. Discussion

It was previously showed that while some patients with mCRC may benefit from curative surgical excision of the primary tumor while other groups might have

more benefits from starting chemotherapeutic strategies first without surgery. So, therapy for mCRC must be individualized for each patient to have optimum results [6]. Between resection of the primary tumor followed by chemotherapy and initial chemotherapy only without surgical intervention has remained controversial for the management of colorectal cancer patients who initially presented with metastasis regarding oncologic outcomes [9].

The principal results shown by our study were that mCRC patients who underwent surgical removal of the primary tumor followed by chemotherapy had a significantly favorable outcome and better survival rate in comparison to patients who have received initial chemotherapy as the 1<sup>st</sup> line of therapy, which is similar to results of previous studies [6] [9].

Xu *et al.*, and KIM *et al.*, agreed with us and revealed that primary tumor resection was a good prognostic parameter for survival rates in mCRC patients [10] [11]. There are several logic and expected explanations for those findings. First, there is higher liability of response to chemotherapy after decreasing tumor mass [12], which was demonstrated by the detected benefit of excision of the primary cancers in the kidney and the ovary in case of presence of metastases [13] [14]. Second, patients with resected primary tumors have less incidence of developing develop obstruction and perforation which is associated with high operative morbidity and mortality [15].

Third, surgical resection of the primary tumor in mCRC might lead to restoration of immune-defense [16]. Additionally the benefit of surgical resection of the primary tumor increased with the addition of novel chemotherapeutic options. Similar to our results there are several retrospective studies [17] [18] [19] [20] [21] and a meta-analysis [15] have showed an improvement in the rates of survival of mCRC patients who underwent surgical removal of the primary tumor followed by chemotherapy in comparison with those managed initially with chemotherapy. Recently KIM *et al.*, [11], clarified the better surgical outcome due to better surgical techniques and improvement of the postoperative care.

Poultides *et al.* [22] study showed results that are different from ours as they have encouraged giving initial chemotherapy without surgical removal of cancer for management of mCRC patients in case of low complication rate of the primary tumor.

Sudo *et al.* [16] provided criteria for management of mCRC and they demonstrated the benefits of aggressive surgical resection in giving better prognosis.

Simillis *et al.* [23] recommended initial systemic chemotherapy for unresectable cases of mCRC as the survival advantages of primary tumor removal was limited and still controversial. With advances in chemotherapy and addition of novel targeted therapeutic agents as cetuximab to the currently used therapies have increased rates of response that resulted in improved overall survival rates for patients with mCRC.

Different results were found by Hu *et al.* [10] showed that the relative improvement of the survival rate of mCRC patients was due to reduction in the

rate of resection of the primary tumor. There are several studies demonstrated that resection of primary tumors, if compared to chemotherapeutic strategies, is not associated with improved patients [24] [25]. Moreover, removal of the primary tumor could stimulate growth of metastases through removal of the metastatic-inhibiting factors or inhibiting the immune responses which is promoted by the primary tumor [26].

**In summary**, CRC patients who were diagnosed initially with synchronous distant metastases who underwent resection of the primary tumor and followed by chemotherapy have a favorable outcome and survival rates when compared to mCRC patients that have received chemotherapeutic agents as the first management line of therapy.

Future prospective studies are required to confirm our significant promising results.

### Limitations of the Study

A small number of patients and short follow-up time are the limitations.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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