Original Article

Retrospective Cohort Study of Primary Tumor Resection in Asymptomatic Stage IV Colorectal Cancer with Irresectable Metastases

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Background: Management of asymptomatic stage IV colorectal cancer (CRC) with irresectable metastases remains controversial.

Objective: The study compared treatment outcomes between primary tumor resection (PTR) and no primary tumor resection (no PTR) in asymptomatic stage IV CRC patients with irresectable metastases.

Materials and Methods: Retrospective cohort study of asymptomatic stage IV CRC patients between 1 September 2006 and 31 August 2016. The inclusion criteria were asymptomatic stage IV CRC, histologically confirmed adenocarcinoma from primary tumor, patients age ≥18 years old, no primary tumor-related symptoms, and Eastern Cooperative Oncology Group (ECOG) performance status 2 or below. The exclusion criteria were symptomatic primary tumors such as bleeding, obstruction, and perforation that required surgery, resectable metastases, and patients with secondary cancer that was diagnosed within 5 years. Primary outcomes were complications that related to primary tumor, such as obstruction, perforation, bleeding, and severe tenesmus, and metastatic complications of cancer. Secondary outcome was median survival time.

Results: There are 135 asymptomatic stage IV CRC patients with irresectable metastases in this study. Complications from primary tumor occurred in 9 (10.98%) and 26 (49.06%) patients in PTR and no PTR groups (p<0.001), respectively. Metastatic complications of cancer occurred in 33 (40.24%) and 19 (35.85%) patients in PTR and no PTR groups (p=0.718), respectively. The median survival time in asymptomatic stage IV colorectal cancer with irresectable metastases was 46.45 months.

Conclusion: The data of no PTR group shows statistically significant complications from primary tumor compared with PTR group. However, there is no statistically significant difference in metastatic complications of cancer in both groups.

Keywords: Stage IV colorectal cancer; Primary tumor resection; Metastases; Colectomy; Synchronous metastases

J Med Assoc Thai 2021;104(Suppl.5): S48-53
Website: http://www.jmatonline.com

Colorectal cancer (CRC) contributes to many cancer-related deaths despite sustained progress in diagnostic and treatment options. Over 20% of patients are first diagnosed at an advance stage, and 70 to 80% of patients presented with irresectable metastasis[1]. The standard treatment in this group is systemic chemotherapy. The indications for surgery are symptomatic complications of primary tumors such as bleeding, obstruction, and perforation. The effectiveness of primary tumor resection (PTR) for asymptomatic stage IV CRC patients to continue prolonged and safe systemic chemotherapy needs to be re-evaluated. PTR may improve survival, but postoperative complications lead to a prolonged hospital stay and delay systemic treatment, which could result in a poor oncologic outcome[2]. Moreover, resection did not significantly reduce the risk of complications from the primary tumor[3].

Some studies have advocated the removal of the primary tumor to allow better survival and fewer complications[4,7-10]. However, many studies[5] concluded that PTR in asymptomatic patients with irresectable stage IV CRC who were managed with chemotherapy or radiotherapy were not associated with a consistent improvement in overall survival.

Management of asymptomatic colorectal cancer (CRC) with irresectable metastases remains controversial. The purpose of this study is to compare treatment outcomes between primary tumor resection (PTR) and no PTR in asymptomatic stage IV CRC patients with irresectable metastases.

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How to cite this article:

Seehawong U, Palitnonkiat V, Supsamutchai C, Thampongsa T, Chatmongkonwat T, Jirasiritham J, Wilasrusmee C, Choikrua P. Retrospective Cohort Study of Primary Tumor Resection in Asymptomatic Stage IV Colorectal Cancer with Irresectable Metastases. J Med Assoc Thai 2021;104 (Suppl.5): S48-53

doi.org/10.35755/jmedassocthai.2021.S05.00071

Materials and Methods

The data were collected from electronic medical records of stage IV CRC patients with irresectable metastases between 1 September 2006 and 31 August 2016.

This study was registered at clinicaltrial.gov (NCT04334395). The inclusion criteria were asymptomatic stage IV CRC, histologically confirmed adenocarcinoma from primary tumor, patients' age ≥18 years old, no primary tumor-related symptoms, and Eastern Cooperative Oncology Group (ECOG) performance status 2 or below. The exclusion criteria were symptomatic primary tumors such as bleeding, obstruction, and perforation that required surgery, resectable metastases, and patients with secondary cancer that was diagnosed within 5 years.

There were 207 patients with stage IV CRC, 27 patients with symptomatic primary tumors, and 45 patients with resectable metastases who were excluded. Therefore, there were 135 patients with asymptomatic primary tumor and irresectable metastases who were included in the analysis (Figure 1).

In this study, the patients were classified into primary tumor resection group (PTR) and no primary tumor resection group (no PTR). Primary tumor resection was defined as partial, subtotal, or total colectomy; proctectomy; or total prontocolectomy without partial or total removal of other organs. No PTR was defined as no surgery, local tumor destruction, or excision.

Primary outcome was complications that related to primary tumor, such as obstruction, perforation, bleeding, and severe tenesmus, and metastatic complications of cancer. Secondary outcome was median survival time, which was defined as time from diagnosis to death or to the last follow-up visit.

Statistical analysis

Basic demographic data were divided into two groups: patients who underwent PTR and no PTR groups. The data are presented in the table format and shown the proportion of data in each group. Additionally, t-test was used as parametric tests for continuous data that had a normal data distribution and descriptive statistics provided a summary of outcomes in the form of mean and standard deviation (SD). The survival rate was calculated by using a Kaplan-Mayer analysis, and a log-rank test was used to compare between groups. In each group, Pearson's Chi-square and Fisher's exact test were used to compare the proportions between two or more categorical variables. A p-value of less than 0.05 was considered to be significant. All data were analyzed with the statistical software "STATA" version 14.0 for window (StataCorp LLC, College Station, Texas, USA).

This study was approves by ethics committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (No. MURA2019/112).

Results

One hundred and thirty-five asymptomatic stage IV CRC patients with irresectable metastases between 1 September 2006 and 31 August 2016 were included in this study. They were classified in two groups as followed: PTR group 82 patients (male=51, female=31) and no PTR group 53 patients (male=33, female=20). The mean age was 62.85±12.95 and 59.59±12.86 years old in PTR

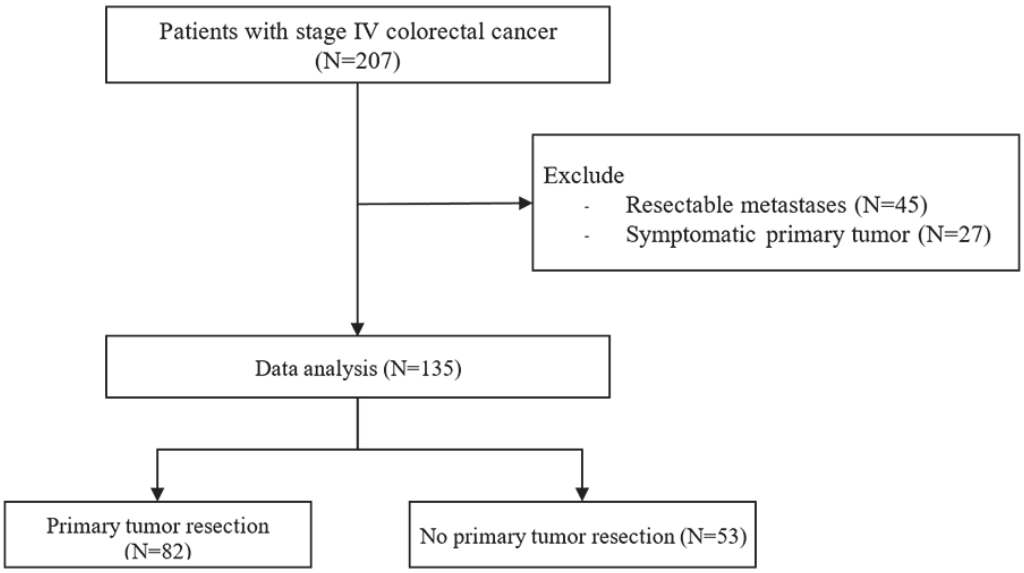

Figure 1. Protocol flow chart of the selection process of the study.

and no PTR groups, respectively. Presenting symptoms were abdominal mass, abdominal pain, gastrointestinal bleeding, bowel habit change, tenesmus, incidental finding from health check-up, and other symptoms. Presenting symptoms from history taking may be recorded more than one symptom. The locations of primary tumor were ascending and transverse colon , descending and sigmoid colon, upper and mid rectum, and lower rectum. As mention above, the number of patients in PTR group were 28 (34.15%), 35 (42.68%), 11 (13.41%), and 8 (9.76), respectively. In no PTR group, the number of patients were 3 (5.66%), 8 (15.09%), 25 (47.17%), and 17 (32.08%), respectively. The organs of metastasis were lung, liver, peritoneal nodule, brain, and bone. Referring to those organs of metastases, the number of patients in PTR group were 14, 59, 16, 0, and 2, respectively. In no PTR group, the number of patients were 27, 42, 6, 1, and 1, respectively. There were 69 (89.61%) and 49 (94.23%) patients received systemic chemotherapy in PTR and no PTR groups, respectively (Table 1).

Postoperative complications in asymptomatic stage IV colorectal cancer (CRC) with irresectable metastases in PTR group occurred in 24 patients (29.27%). There were surgical site infection 8 patients (9.76%), intra-abdominal collection 2 patients (2.44%), anastomosis leakage 4 patients

Table 1. Characteristic data

	Primary tumor resection (n=82)	No primary tumor resection (n=53)	Total (n=135)	p-value
Age: mean (SD)	62.85 (12.95)	59.59 (12.86)	61.57 (12.97)	0.154
BW (kg): median (iqr)	61 (18.42)	62.5 (19.4)	61 (18.42)	0.913
Sex: n (%)				
Male	51 (62.20)	33 (62.26)	84 (62.22)	0.999
Female	31 (37.80)	20 (37.74)	51 (37.78)	
Presenting symptoms				
Abdominal mass	8 (9.76)	2 (96.23)	10 (7.41)	0.315
Abdominal pain	30 (36.59)	13 (24.53)	43 (31.85)	0.186
GI bleeding	26 (31.71)	23 (43.40)	49 (36.30)	0.201
Bowel habit change	27 (32.93)	19 (35.85)	46 (34.07)	0.853
Tenesmus	1 (1.22)	8 (15.09)	9 (6.67)	0.002
Check-up	1 (1.22)	1 (1.89)	2 (1.48)	0.999
Other	11 (13.41)	1 (1.89)	12 (8.89)	0.028
Location of primary tumor				
Ascending colon & transverse colon	28 (34.15)	3 (5.66)	31 (22.96)	<0.001
Descending colon & sigmoid colon	35 (42.68)	8 (15.09)	43 (31.85)	
Upper & mid rectum	11 (13.41)	25 (47.17)	36 (26.67)	
Lower rectum	8 (9.76)	17 (32.08)	25 (18.52)	
Organ of metastasis				
Lung	14 (17.07)	27 (50.94)	41 (30.37)	<0.001
Liver	59 (71.95)	42 (79.25)	101 (74.81)	0.418
Peritoneal nodule	16 (19.51)	6 (11.32)	22 (16.30)	0.241
Brain	0	1 (1.89)	1 (0.74n)	0.393
Bone	2 (2.44)	1 (1.89)	3 (2.22)	0.999
Histological subtype from primary tumor				
Classic adenocarcinoma	80 (97.56)	52 (98.11)	132 (97.78)	0.242
Mucinous adenocarcinoma	2 (2.44)	0 (0)	2 (1.48)	
Signet-ring cell carcinoma	0 (0)	0 (0)	0 (0)	
Adenocarcinoma with mixed subtypes	0 (0)	1 (1.89)	1 (0.74)	
Systemic chemotherapy	69 (89.61)	49 (94.23)	118 (91.47)	0.524

BW = body weight; SD = standard deviation

(4.88%), lung complication 2 patients (2.44%), pulmonary embolism 1 patient (1.22%), wound dehiscence 1 patient (1.22%), and other complications 6 patients (7.32%) (Table 2).

Complications from primary tumor occurred in 9 (10.98%) and 26 (49.06%) patients in PTR and no PTR groups, respectively (p<0.001). Gut obstruction was found in 2 (2.44%) and 10 patients (18.87%) in PTR and no PTR groups, respectively (p=0.002). Bleeding was found in 1 (1.22%) and 11 patients (20.75%) in PTR and non PTR groups, respectively (p<0.001). Severe tenesmus was found in 3 (3.66%) and 2 (3.77%) patients in PTR and no PTR groups, respectively (p=0.999). Other complication from primary tumor was found in 2 (2.44%) and 4 (7.55%) patients in PTR and no PTR groups, respectively (p=0.210). Metastatic complications of cancer were found in 33 (40.24%) and 19 patients (33.33%) in PTR and no PTR groups, respectively (p=0.718) (Table 3).

The median survival time in asymptomatic stage IV colorectal cancer with irresectable metastases was 46.45 months (Figure 2).

Discussion

This study showed two key results. First, there was statistically significant difference in complication from primary tumor in PTR and no PTR groups. Second, metastatic complications of cancer were not statistically different in PTR and no PTR groups.

It is controversial whether systemic chemotherapy with or without primary tumor resection was effective for the patients with incurable Stage IV CRC. Some studies have reported that there was a benefit of primary tumor resection on overall survival[4-7]. While some other studies found that there was no statistically significant difference in the median in overall survival in both groups. However, a meta-analysis study[8] found that PTR in metastasis CRC had a better overall survival than no PTR. Patients treated with chemotherapy had 7.3-times more complications than PTR. Venderbosch, et al[9] reported that PTR had a better survival rate than no PTR i.e., 16.7 vs. 11.4 months, respectively, in the CAIRO study and 20.7 vs. 13.4 months, respectively, in the CAIRO2 study. De Meistier, et al[10] reported that PTR had better overall survival than no PTR. The benefit of PTR was found in a subgroup of patients whose age were less than 70 years old, with a WHO performance status <2, no extrahepatic metastasis, and liver tumor burden of less than 50%.

However, a Cochrane review[11] concluded that PTR in asymptomatic patients with irresectable stage IV CRC who were managed with chemotherapy or radiotherapy

Table 2. Post-operative complications in primary tumor resection (PTR) group

Post-operative complications	Primary tumor resection (n=82)
Surgical site infection	8 (9.76)
Intra-abdominal collection	2 (2.44)
Anastomosis leakage	4 (4.88)
Lung complication	2 (2.44)
Pulmonary embolism	1 (1.22)
Wound dehiscence	1 (1.22)
Others	6 (7.32)
Total	24 (29.27)

Table 3. Complications from primary tumor and metastatic cancer in primary tumor resection (PTR) and no primary tumor resection (no PTR) groups

	Primary tumor resection (n=82)	No primary tumor resection (n=53)	Total (n=135)	p-value
Complications from primary tumor	9 (10.98)	26 (49.06)	35 (25.93)	<0.001
Symptoms				
Obstruction	2 (2.44)	10 (18.87)	12 (8.89)	0.002
Bleeding	1 (1.22)	11 (20.75)	12 (8.89)	<0.001
Severe tenesmus	3 (3.66)	2 (3.77)	5 (3.70)	0.999
Other	2 (2.44)	4 (7.55)	6 (4.44)	0.210
Metastatic complications of cancer	33 (40.24)	19 (35.85)	52 (38.52)	0.718
Symptoms				
Dyspnea	3 (3.66)	3 (5.66)	6 (4.44)	0.679
Liver failure	11 (13.41)	3 (5.66)	14 (10.37)	0.247
Bleeding	1 (1.22)	0 (0)	1 (0.74)	0.999
Bone pain	4 (4.88)	4 (7.55)	8 (5.93)	0.711
Other	1 (1.22)	0 (0)	1 (0.74)	0.999

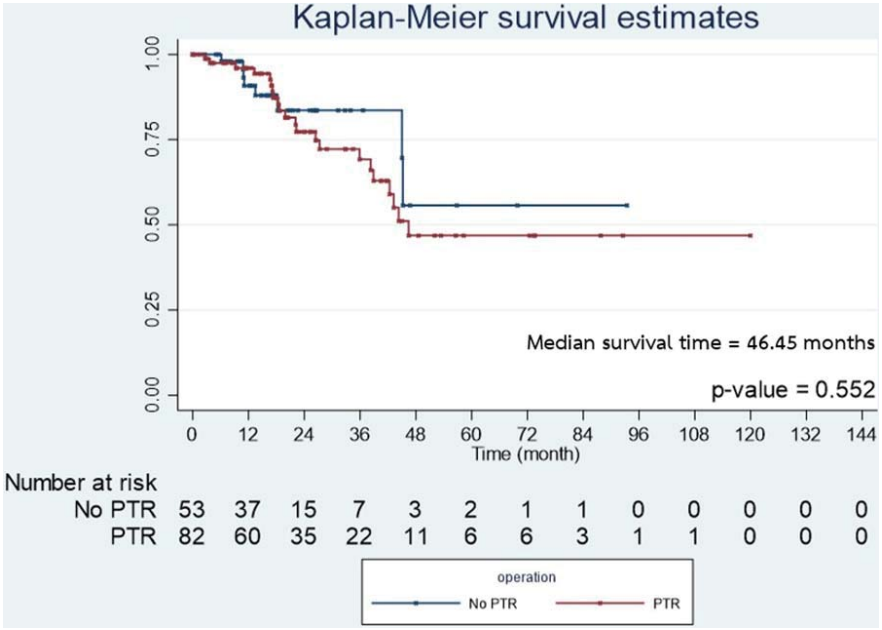

Figure 2. Kaplan-Meier survival graph of the PTR and no PTR groups.

were not associated with a consistent improvement in overall survival. Moreover, resection did not significantly reduce the risk of complications from the primary tumor[3]. Additionally, 8% of patients developed symptoms that required palliative surgery compared to around 20% morbidity in the surgery group[12]. This study showed morbidity and mortality related to tumor resection, so it should be avoided because of delaying initiated chemotherapy. The results of this study did not support the benefit of PTR on patient survival, which was similar to studies by Zeinab[13] and Benoist, et al[14].

Conversely, many studies reported that primary tumor resection is necessary in patients with irresectable metastases and an asymptomatic primary tumor[15]. The result of the present study showed that primary tumor resection could prevent complications in primary tumor, especially intestinal obstruction and bleeding. PTR for asymptomatic stage IV CRC patients showed an acceptable prognosis in appropriate selected patients.

There are some limitations in this study. Firstly, it was a retrospective study that might have selection bias such as the criteria for choosing each treatment modality. Secondly, the small population size in each group might affect the statistical significance. Lastly, the treatment modalities in retrospective data might be heterogenous.

Conclusion

The data of no PTR group shows statistically significant complications from primary tumor compared with PTR group. However, there is no statistically significant difference in metastatic complications of cancer in both groups. The management of asymptomatic stage IV colorectal cancer (CRC) with irresectable metastases remains controversial. Primary tumor resection for asymptomatic stage IV CRC patients with irresectable metastases showed an acceptable prognosis, and appropriate patient selection is needed to determine its true benefit.

What is already known in this topic?

70 to 80% of patients presented with irresectable metastases and standard treatment in this group is systemic chemotherapy.

Indications for surgery are symptomatic complications of primary tumors such as bleeding, obstruction, and perforation.

Some study show PTR may improve survival, but postoperative complications lead to a prolonged hospital stay and delay systemic treatment, which could result in a poor oncologic outcome.

No consensus on the appropriate management of asymptomatic and minimally symptomatic patients with stage IV CRC and irresectable metastases.

What this study adds?

There is no statistically significant and clinically relevant survival benefit was found in patients who underwent PTR in our cohort from 2006 to 2016.

Complications such as obstruction and bleeding

occurred more often in the no PTR compared to the PTR group.

Primary tumor resection in asymptomatic stage IV CRC patients with irresectable metastases showed an acceptable prognosis, and appropriate patient selection is needed to determine its true benefit.

Acknowledgements

We wish to acknowledge Mr. Napaphat Poprom for statistical analysis of the text.

Potential conflicts of interest

The authors declare no conflict of interest.

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