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ORIGINAL ARTICLE

The role of primary tumor resection in patients with stage IV colorectal cancer with unresectable metastases

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Summary

Purpose: *Whether primary tumor resection (PTR) should be performed in patients with asymptomatic colorectal cancer (CRC) and unresectable synchronous metastasis is controversial. The purpose of this study was to investigate the prognostic impact of initial primary tumor resection in pa-tients with synchronous unresectable metastatic CRC.*

Methods: *The patients with unresectable synchronous metastatic CRC who had undergone primary tumor resection and then received chemotherapy were compared with the patients who received only palliative systemic chemotherapy.*

Results: *Survival analysis showed that median overall survival (OS) for all patients was 22.37 months. Primary tumor resection was associated with a significant survival benefit on unadjusted analysis (median survival 29.56 months vs. 14.25 months; p<0.001). Two-year, 3-year and 5-year survival rates were 57%, 35%, 19% for the PTR group and 30%, 16%, 8% for the non-PTR group and all results were statistically significant and favored surgery.*

Conclusions: *Our study suggests that primary tumor resection improves the survival of patients with metastatic CRC and unresectable synchronous metastasis.*

Key words: *metastatic colorectal cancer, primary tumor resection, chemotherapy*

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide [1]. Approximately 20% of CRC patients are diagnosed with stage IV disease, and about 75% to 90% of these patients have unresectable metastatic lesions [2-5]. Primary tumor resection (PTR) is the only curative treatment in earlier stages of colon cancer. PTR is not considered curative for patients who present with stage IV disease unless it is performed with simultaneous resection of all metastatic disease. In this setting, the treatment is palliative and based on systemic chemotherapy and biotherapy; the main purpose is to improve survival and the quality of life. PTR is only indicated for palliation of symptoms of obstruction, perforation, or intractable bleeding.

Although PTR is not recommended in patients with asymptomatic CRC and unresectable synchronous metastasis, some large population-based studies and literature reviews have shown that palliative resection of asymptomatic primary tumors helps prolong overall survival [6-10]. But all this data is retrospective and has many limiting selection biases. There are no prospective randomized clinical trials been reported to date.

In this study, we retrospectively investigated the role of the PTR in patients with synchronous unresectable metastatic CRC in our patient group.

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Methods

Patients

We enrolled and studied retrospectively 215 consecutive patients with stage IV synchronous unresectable metastatic CRC who were treated with systemic chemotherapy at Kayseri Acibadem Hospital and Ankara Numune Educational and Research Hospital between 01.06.2009-31.12.2016. Patients have been followed until 1 March 2019.

Patients were divided into two groups as primary tumor resection (PTR) group and non-PTR group. Patients who were operated at the time of diagnosis and then received chemotherapy (FOLFIRI or FOLFOX/XELOX) ±molecular targeted agents (bevacizumab or cetuximab/panitumumal) were placed in the PTR group. Patients treated with only palliative systemic chemotherapy±molecular targeted agent without primary surgery were divided into the non-surgical group.

Data collected from patient records included demographic data (sex, age, and body mass index (BMI), Eastern Cooperative Oncology Group Performance status (PS), tumor-specific data (including location, metastatic sites), chemotherapy and targeted therapy agents and survival.

Endpoints

The primary endpoint was overall survival (OS), defined as the time of death or last follow up from the time of diagnosis. Secondary endpoints were progression free survival (PFS) and 2,3 and 5-year OS rates. PFS shows the time of progression, death or last follow up from the beginning of the first chemotherapy cycle. Endpoint was set at March 1st 2019.

Statistics

Statistical analyses were performed using SPSS 22.0 software (IBM,USA). PFS was considered as the duration between chemotherapy and radiologic progression or death and was calculated using the Kaplan-Meier method while log rank test was performed to assess differences. To determine the relationship between variables, Pearson's correlation coefficient was used. A p value <0.05 was considered as statistically significant in all calculations.

Results

Patient characteristics

215 patients were included for final analyses. Surgery was performed in 139 patients (65%) wheras the primary tumor was left in place in the remaining 76 (35%). The patients included were 136 men and 79 women with a median age of 60 years (range 22-86). Most of the patients had ECOG PS 0-1. Sixty two of the patients had tumor located in the right side (hepatic flexure through cecum), and 147 in the left side (splenic flexura to rectum); tumor location information of 6 patients was lacking in the files.

Table 1. Demographics and baseline characteristics of patients

Characteristics	*Primary surgery*	*Non-surgery*	*p value*
Total	139	76	
Gender			0.237
Male	85	51	
Female	54	25	
Age, years (median; range)	59 (22-85)	62 (27-86)	0.286
BMI			0.465
Underweight	4	2	
Normal	48	27	
Overweight	72	27	
ECOG PS			0.119
0-1	101	44	
2	14	13	
Localization			0.049
Right	46	16	
Left	90	57	
Stage			0.074
4A	75	49	
4B	25	14	
4C	39	13	
CT+Bevacizumab	93	55	0.348
Chemotherapy only	37	17	0.348

With regard to metastasis, patients were divided in three stages according to new NCCN staging system. One hundred and twenty four patients were in stage 4A (metastatis to one site organ without peritoneal metastasis) ; 40 patients were in stage 4B (metastasis to two or more sites or organs without peritoneal metastasis); and 51 patients were in stage 4C (metastasis to peritoneal surface alone or with other site or organ metastasis). Liver was the most common metastatic site (80%) followed by peritoneum and lungs (24% and 21%,respectively). 117 patients (54%) had isolated liver metastasis. The clinical features of the patients were similar in both groups and the characteristics at baseline are shown in Table 1.

Treatments received

All patients receiving a first line chemotherapy after upfront surgery or not, was the main inclusion criterion of the study. First line bevacizumab administration characteristics (66.9% in the surgery group and 72.3% in the non-surgery group, p=0.348) were similar between the two groups. Anti-EGFR use was very restricted due to patient inclusion dates. Only 13 patients had used anti-EGFR agent (panitumumab or cetuximab) combination with chemotherapy; 9 were in the surgery group and 4 were in the non-surgery group. Overall, 65% of all patients, 73% of the surgery group and 61.3% of the non-surgery group received second line chemotherapy, respectively.

Survival analysis

Median follow-up was 24.57 months (range 1.05-105.46). On March 1st, 2019, 183 patients (85%) had died: 107 (78%) in the surgery group and 76 (100%) in the non-surgery group.

Survival analysis showed that the median OS

Table 2. Overall survival

	Surgery (%)	*Non-surgery (%)*	*p value*
2 -year OS	57	30	0.02
3-year OS	35	16	0.03
5-year OS	19	8	0.02

Table 3. Survival according to subgroups

	Median OS (months)		
	Surgery	*Non-surgery*	*p value*
All patients	29.5	14.2	<0.001
Sex			
Male	27.82	14.25	<0.001
Female	31.67	13.83	0.03
Age, years			
<65	28.41	17.84	<0.012
>65	33.9	7.39	<0.001
ECOG PS			
0-1	30.39	14.62	<0.001
2	18.99	14.25	0.98
BMI			
Normal	30.39	12.35	<0.001
Owerweight-obese	31.50	19.51	0.002
Tumor side			
Right	23.7	7.81	0.029
Left	32.3	19.5	<0.001
Stage			
4A	31.7	18.5	0.001
4B	19.5	13.2	0.04
4C	34.2	12.3	0.003
Treatment			
Chemotherapy+Bevacizumab	24.5	13.8	<0.001
Chemotherapy only	23.2	12.2	0.002

for all 215 registered patients was 22.37 months. Survival was 29.56 months in the PTR group and 14.25 months in the non-PTR group (p<0,001). Two-year, 3-year and 5-year OS were 57%, 35%, 19% for the PTR group and 30%, 16%, 8% for the non-surgical group and all results were statistically significant and favored surgery (Table 2).

Survival results were better in patients with tumor located in the left colon than right colon in both surgery and non-surgery group. Median OS was 23.7 months for right colon surgery group while median OS was 7.8 months with right colon non-surgery group (p=0.029). Median OS was 32.5 months for left colon surgery group and 19.5 months for left colon non-surgery group (p<0.001) (Table 3).

Surgery gave superior results than non-surgery in stage 4A and 4C patients, while the results were similar in stage 4B patients. Median OS was 31.7 months and 18.5 months in the 4A PTR and non-PTR group (p=0.001), 19.5 months and 13.2 months in the 4B PTR and non-PTR group (p=0.59) and finally 34.2 months and 12.3 months for stage 4C PTR and non-PTR group (p=0.003) (Table 3).

Surgery was shown to improve survival independently of treatment. OS was 24.5 months vs 13.8 months in the PTR and non-PTR group who were treated with chemotherapy+ bevacizumab (p=0.001), whereas OS was 35.6 months vs 22.2 months in the PTR and non-PTR group who were treated with chemotherapy alone (p=0.002). Since the number of patients receiving panitumumab was very small, it was not included in the statistical evaluation (Table 3).

Median progression free survival (PFS) was 9.85 months and 7.06 months in the surgery and non-surgery group (p=0.001).

Seven of the 76 patients who had not been operated died due to primary tumor-related complications (5 of them were due to ileus, 1 to perforation and 1 to bleeding). Four of them were right-sided and three were left-sided tumors.

Discussion

Recent advancements in chemotherapeutic and new molecular targeted agents have extended survival in patients with stage IV CRC. Nevertheless, overall prognosis remains poor with a 5-year OS of only 8-20% [2,3]. In metastatic colon cancer, indications for radical resection of the primary tumor include bleeding, obstruction and perforation. Without these indications, survival benefit of PTR has been controversial [6-12]. Potential benefits from resection of the primary tumor must be weighed against the morbidity and mortality that would be associated with surgery.

So far, there is no any published prospective randomized clinical trial showing the effectiveness of surgery, while several retrospective series or meta-analyses have been published. Most of these studies demonstrated a significant correlation between longer survival and primary tumor resection compared to conservative management [6-10,13-15]. In a meta-analysis of studies including a total of 43,903 patients, Lee et al reported longer OS in patients who underwent primary tumor resection plus chemotherapy/radiotherapy (p<0.001); median OS was found between 4-30.7 months in patients who underwent primary tumor resection and 2-23.9 months in patients without primary tumor resection. In this meta-analysis, among the patients receiving chemotherapy with or without bevacizumab/cetuximab targeted therapy agents, survival in the PTR arm was longer, independent of the given treatment (p<0.001 for chemotherapy; p<0.003 for chemotherapy + targeted agents) [6]. Similarly, in our study PTR was still effective in patients treated with chemotherapy or chemotherapy + bevacizumab compared with non-PTR. Another meta-analysis of 21 studies including 44,226 patients, Clancy et al found that primary tumor resection in patients with unresectable metastasis was associated with a lower risk of mortality compared with chemotherapy alone, with a difference in 6.4-month mean survival in favor of resection (p<0.001) [8]. Konyalian et al found that survival was increased in patients undergoing surgery compared to patients treated with non-surgical methods (p<0.0001) and after age, gender, tumor location and liver involvement were controlled; patients with tumor resection still survived longer (H=0.34; 95% CI:0.21-0.559) [10], as in our study. On the contrary, some studies have proposed that survival of CRC patients with unresectable synchronous metastasis is not prolonged with PTR. Scogins et al examined 89 asymptomatic patients with primary colorectal tumors who presented with incurable metastatic disease and found the median survival in the non-resection group was 16.6 months and in the resection group it was 14.5 months (p=0.59) [16]. In another study in a similar patient population the median survival of patients in the unresected group was 8.2 months compared with 14.0 months for the resected group; however, it was not significantly associated with survival (p=0.08) [17]. Alawadi et al performed an observational cohort study on patients with unresectable metastatic colon cancer that were identified from the National Cancer Data Base (2003-2005). Among patients with unresectable metastatic colon cancer, after the confounder effects were adjusted, PTR was not correlated with improved survival compared to systemic chemotherapy [18].

In previous studies and meta-analyses, it is seen that patients with different metastatic spread patterns were analyzed together. This is the first study that differentiates patients to M1a, M1b, M1c according to the new staging system and investigating survival data of PTR. According to our findings, PTR was statistically effective in all patients in stage 4A, 4B and 4C (p=0.001, p=0.04 and p=0.003 respectively). Peritoneal carcinomatosis is associated with a significantly shorter OS and PFS as compared with those without metastatic peritoneal carcinomatosis of CRC [19,20] and staged as M1c in the 8th edition of the AJCC Cancer Staging Manual [21]. Costi et al included 130 patients in their study who were classified according to the metastatic pattern. Resective procedures were associated with longer median OS than non-resective procedures (9 months vs 3 months), but no statistically significant difference was observed for patiens with peritoneal carcinomatosis and distant metastasis (median survival: 8 months vs 0; p=0.009) [22]. The effectiveness of the surgery was independent from the metastatic pattern of the tumor in our study, but OS was 34.2 months in the M1c patients who underwent surgery, higher than expected. The great survival advantage of surgery in this patient group with poor prognosis is amazing and it may be due to the retrospective nature of the study and the small number of patients in the groups.

To summarize, this retrospective cohort of unselected patients with metastatic CRC and unresectable synchronous metastasis, up-front PTR was significantly associated with prolonged OS. Randomized controlled trials, such as synchronous [23] and CAIRO4 [24], are currently ongoing to draw definitive conclusions about this topic and the results are eagerly awaited.

Conflict of interests

The authors declare no conflict of interests.

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