

Does primary tumor resection contribute to overall survival in unresectable synchronous metastatic colorectal cancer?

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Background: Primary tumor resection (PTR) in metastatic colorectal cancer (mCRC) has not been suggested by guidelines, since new systemic chemotherapy options have improved overall survival. However, the effect of PTR is still controversial in mCRC. In this study, we aimed to evaluate the effect of PTR on survival in unresectable mCRC. **Materials and Methods:** Two hundred and fifty-two patients with unresectable mCRC were screened retrospectively between January 2007 and December 2017 and a total of 147 patients who met inclusion criteria were included. The patients with emergency or elective PTR and the patients without surgery were compared for baseline features and overall survival. **Results:** The median follow-up time was 15.6 months (range; 1.2–78.9) in whole patients. There were 91 patients in nonsurgical (NS) group and 56 patients in PTR group. The median overall survival was significantly longer in PTR group compared NS group (21.8 vs. 17.0 months, $P = 0.01$), but it was not associated to better overall survival in multivariate Cox analysis (hazard ratio: 0.65, 95% confidence interval: 0.41–1.02, $P = 0.06$). There was no significant difference in overall survival between emergency and elective surgery subgroups (22.9 vs. 16.1 months, respectively, $P = 0.9$). **Conclusion:** PTR did not offer an overall survival benefit in this study. Although it is debated, we think that it is better to start treatment with chemotherapy and biological agent combinations in patients with asymptomatic mCRC. Thus, the patients can be protected from the morbidity and mortality of the surgery.

Keywords: Colectomy, colorectal cancer, metastatic, palliative surgery, survival

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INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women in the world.^[1] Approximately, 20% of all colorectal cancer patients present with distant metastasis.^[2] The treatment is palliative in most of the patients with metastatic disease, and the goal of treatment is to improve the quality of life and prolong overall survival.^[3] Despite recent advances, 5-year survival in metastatic colorectal cancer (mCRC) is around 12%–13%.^[4] Liver is the most common metastatic site in mCRC. Primary tumor resection (PTR) and metastasectomy were shown to

prolong survival in potentially resectable mCRC.^[5] However, most of the metastatic patients (75%–90%) present with unresectable metastasis.^[6] It is apparent that PTR should be performed in patients with serious bleeding, obstruction or ileus. However, PTR is still debated in asymptomatic patients with unresectable metastasis.

Traditionally, prophylactic resection of primary tumor in asymptomatic patients with unresectable metastatic disease was performed in many patients to avoid late complications such as obstruction, perforation, or bleeding and in order to eliminate chemoresistance.^[6,7] Another view which advocates PTR is to reduce the

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systemic tumor burden with PTR so that survival may be prolonged by reversing systemic inflammation.^[8] However, most of the evidence supporting this strategy is derived from the period of fluoropyrimidine monotherapy which was the standard treatment in the 1990s.^[9] Anymore, it is known that introduction of new agents such as oxaliplatin, irinotecan, cetuximab, and bevacizumab improved overall survival in unresectable mCRC patients independent of PTR.^[10]

On the other hand, exposing increased postoperative morbidity and mortality and loss of time for the onset of systemic therapy are another problem in asymptomatic patients and in the light of new chemotherapies, it is difficult to comment on who will benefit from PTR. So PTR in patients with unresectable synchronous metastasis is still needed to be reevaluated in this way. The aim of the present study is to evaluate the effect of PTR on overall survival in unresectable synchronous mCRC.

MATERIALS AND METHODS

Patient characteristics

Two hundred and fifty-two patients with unresectable mCRC were screened retrospectively between January 2007 and December 2017. A total of 147 patients who underwent emergency or elective R0 PTR or received palliative systemic chemotherapy were included in the study.

Inclusion criteria were defined as: (1) aged ≥ 18 years, (2) histologically confirmed colorectal carcinoma, (3) Eastern Cooperative Oncology Group-Performance Score (ECOG-PS) ≤ 2 , (4) measurable unresectable metastatic disease according to response evaluation criteria in solid tumors (RECIST), and (5) having normal liver, bone marrow, and kidney function. The patients were excluded if they had brain metastasis, metastasectomy with the curative intent, R1/R2 PTR, and palliative colostomy operation.

Criteria for unresectability for metastatic disease were defined as: (1) those who do not meet the criteria for liver resectability^[11] (suitable for R0 resection, preservation of two adjacent segments, preservation of biliary drainage, adequate remnant liver tissue more than 20%, and potentially resectable extrahepatic metastasis), (2) those who do not meet the criteria for lung resectability^[12] (suitable for R0 resection based upon computed tomography, adequate cardiopulmonary reserve to tolerate resection, potentially resectable extrapulmonary metastasis), (3) peritoneal metastasis, and (4) bone metastasis. Number or size limitation was not made for metastasectomy.

Clinicopathologic features (age, gender, ECOG-PS, body mass index [BMI], KRAS mutation status, tumor

localization, pathological subtype, number of metastatic sites, localization of metastasis [liver, lung, and peritoneum], type of operation [emergency or elective], number of chemotherapy lines [2 or ≥ 3], and systemic treatment agents) were recorded. Operation-related morbidity analysis could not be performed due to the lack of data.

Patients were grouped as palliative PTR (with chemotherapy) versus palliative systemic chemotherapy (nonsurgical [NS]). Patients with PTR were evaluated as emergency or elective subgroups and compared with NS group. The operation which was performed because of bleeding, perforation, or ileus was defined as emergency. PTR which was done because of inadequate staging before surgery in the metastatic setting and those performed with surgeon's preference (in order to prevent future complications) despite known metastatic stage were defined as elective operation.

Tumor response was assessed by computerized tomography or positron emission tomography/computed tomography according to the RECIST criteria (v1.1). According to RECIST criteria, complete response was defined as disappearance of all target lesions and reduction of all pathologic lymph nodes to ≤ 10 mm (short axis), partial response was defined as $\geq 30\%$ decrease in tumor size, progressive disease was defined as $\geq 20\%$ increase in tumor size, stable disease is neither partial response nor progressive disease criteria met. Disease control rate was defined as the sum of complete response, partial response, and stable disease rates.

Prognostic factor analysis

Fourteen variables were selected based on previous studies which may have an effect on overall survival.^[6,7] Variables were divided into two categories: age (< 65 or ≥ 65 years), gender (male or female), ECOG-PS (0 or 1–2), BMI (< 25 kg/m² or ≥ 25 kg/m²), tumor localization (right or left, rectum, or colon), histological subtype (adenocarcinoma or mucinous carcinoma), KRAS mutation status (mutant or wild), number of metastatic sites (1 or ≥ 2), liver metastasis (presence or absence), lung metastasis (presence or absence), peritoneal metastasis (presence or absence), first-line chemotherapy regimen (oxaliplatin or irinotecan), and first-line biological agent type (anti-vascular endothelial growth factor [anti-VEGF] or anti-epidermal growth factor receptor [anti-EGFR]).

Statistical analysis

The statistical software package SPSS version 22.0 (SPSS, Chicago, IL, USA) was used for all analyzes in this study. The Pearson Chi-square or Fisher's exact test was used to evaluate the differences between the categorical groups. When the Chi-square test of a table larger than 2×2 was significant ($P < 0.05$), *post hoc* test was used with Bonferroni correction method. Overall survival was defined as the time

from the diagnosis of synchronous mCRC to death from any cause or censoring. Survival analysis was performed with the Kaplan–Meier method using log-rank test (95% confidence interval [CI]). The variables identified with a $P < 0.10$ from univariate analysis were included in the multivariate model. Using Schoenfeld residuals, assumption of proportional hazards (PH) was tested. Cox regression model was used to find independent prognostic factors for overall survival if the PH assumption was met. If not met, accelerated failure time models were used. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Median age was 56 years (range; 25–80). There were 91 (62%) patients (male: female = 2:1) in the NS group and 56 patients (male: female = 1.8:1) in the PTR group. Left-sided tumors (81% and 66%, respectively, $P = 0.03$) and liver metastasis (89% and 67%, respectively, $P = 0.001$), were higher in NS group, whereas peritoneal metastasis was more frequent in the PTR group (16% and 31%, respectively, $P = 0.04$). A *post hoc* z-test on the adjusted residuals with Bonferroni correction which was done for tumor localization revealed that there was a significant difference between the groups only in terms of rectum ($P = 0.007$). PTR and NS groups were not significantly different in terms of other baseline features. Clinicopathological and treatment features of the patients were summarized in Table 1. In the PTR group, the surgical procedures were right hemicolectomy in 16 patients (29%), left hemicolectomy in 8 patients (14%), sigmoidectomy in 10 patients (18%), low anterior resection in 14 patients (25%), and subtotal colectomy in 8 patients (14%). Also in this group, colostomy/ileostomy was performed in 67% of the patients, and intestinal anastomosis was performed in 33% of the patients.

The median follow-up time was 15.6 months (1.2–78.9) and the median overall survival was 17.9 months (95% CI: 15.1–20.7) in whole patients. There was no difference between PTR and NS groups in terms of progression-free survival (7.5 vs. 6.8 months, respectively; $P = 0.2$). The median overall survival was significantly longer in PTR group compared to NS group (21.8 vs. 17.0 months, $P = 0.01$) [Figure 1]. However, when evaluated by multivariate analysis, the difference was not statistically significant (hazard ratio [HR]: 0.65, 95% CI: 0.41–1.02, $P = 0.06$).

The patients with PTR were evaluated as emergency or elective surgery subgroups and compared with NS group. In the resection subgroups, 54% of patients ($n = 30$) had emergency operation and 46% ($n = 26$) had elective operation. Twenty-two patients underwent elective PTR due to inadequate staging before surgery and four patients

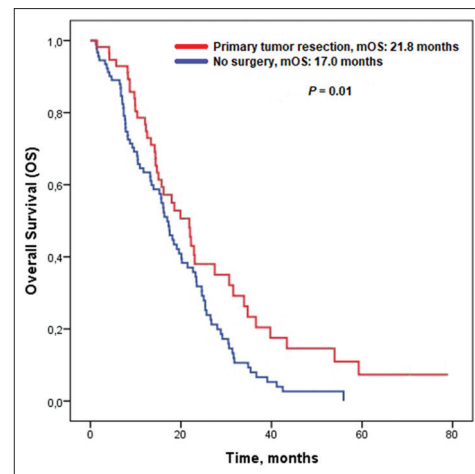


Figure 1: Kaplan–Meier curve for overall survival in all patients

had PTR in order to prevent future complications related to the primary tumor (surgeon's preference). Twenty-three patients in emergency subgroup and all of the patients in elective subgroup underwent PTR before the first-line chemotherapy. The median overall survival was numerically longer, but statistically insignificant in emergency subgroup compared to elective subgroup (22.9 vs. 16.1 months, $P = 0.9$). When emergency resection subgroup was compared to NS group, overall survival was significantly higher in emergency resection subgroup (22.9 vs. 17.0 months, $P = 0.048$) in univariate analysis but not in multivariate analysis (HR: 1.57, 95% CI: 0.88–2.82, $P = 0.1$). Overall survival was similar in elective surgery subgroup and NS group (16.1 vs. 17.0 months, $P = 0.8$) [Figures 2 and 3].

One hundred and twenty-nine patients (88%) received oxaliplatin and 18 patients (12%) received irinotecan-based chemotherapy regimen as the first-line therapy. There was no difference in overall survival in terms of receiving first-line oxaliplatin or irinotecan-based regimen (17.5 vs. 18.6 months, respectively; $P = 0.4$). In the first-line treatment, 28 patients received anti-VEGF agents and 16 patients received anti-EGFR agents. There was no overall survival difference between these groups (18.1 vs. 19.8 months, respectively; $P = 0.8$). The reason for the low number of patients using biological agents in the first-line treatment was that the results of RAS mutation analysis were not known at the beginning of treatment.

Forty-nine patients underwent PTR before the first-line chemotherapy. Complete response in these patients was significantly better compared to NS group (0 and 12%, respectively, $P = 0.001$), but there was no significant difference between the groups in terms of partial response (46% and 47% respectively, $P = 0.8$).

In univariate analysis, the number of metastatic sites (20.2 vs. 15.6 months, $P = 0.02$) and ECOG-PS (22.7 vs. 14.2 months,

Table 1: Baseline characteristics

	No surgery (n=91), n (%)	PTR (n=56), n (%)	P
Age (years)			
Median (range)	56 (25-80)	58 (26-80)	0.5
<65	64 (70)	42 (75)	
≥65	27 (30)	14 (25)	
Sex			
Female	30 (33)	20 (36)	0.7
Male	61 (67)	36 (64)	
ECOG-PS			
0	45 (49)	22 (39)	0.2
1	41 (45)	30 (54)	
2	5 (6)	4 (7)	
BMI (kg/m ²)			
Median (range)	25.6 (18-41)	26 (18-36)	0.6
<25	44 (47)	25 (45)	
≥25	47 (53)	31 (55)	
Tumor localization			
Rectum	42 (46)	15 (27)	0.03
Left	32 (35)	22 (39)	
Right	17 (19)	19 (34)	
Histology			
Adenocarcinoma	85 (93)	47 (84)	0.06
Mucinous carcinoma	6 (7)	9 (16)	
KRAS			
Mutant	36 (40)	25 (45)	0.5
Wild	55 (60)	31 (55)	
Number of metastatic sites			
Single	54 (59)	42 (75)	0.05
Multiple	37 (41)	14 (25)	
Metastatic regions			
Liver	81 (89)	36 (67)	0.001
Lung	25 (28)	10 (18)	0.2
Peritoneum	15 (16)	17 (31)	0.04
Bone	6 (7)	2 (4)	0.4
Operation type			
Emergency		30 (54)	-
Elective		26 (46)	
Systemic anticancer treatment lines (pre-post operation total)			
<3	56 (62)	37 (66)	0.5
≥3	35 (38)	19 (34)	
Treatment agents used (including all lines)			
Oxaliplatin	88 (97)	53 (95)	0.7
Irinotecan	55 (60)	30 (54)	
Anti-VEGF treatment	50 (55)	27 (48)	
Anti-EGFR treatment	32 (35)	13 (23)	

ECOG-PS=Eastern Cooperative Oncology Group-Performance Score; BMI=Body mass index; VEGF=Vascular endothelial growth factor; EGFR=Epidermal growth factor receptor; PTR=Primary tumor resection

$P = 0.004$) were found to be prognostic factors associated with overall survival. Five factors with a $P < 0.1$ were included in the multivariate analysis (BMI, ECOG-PS, number of metastasis sites, liver metastasis, and PTR). To further evaluate whether the PH assumption was valid, Schoenfeld residuals were analyzed with respect to ranked survival time for selected predictors. All fitted lines derived from individual scatter plots seemed to be horizontal.

P values for ECOG-PS, BMI, number of metastatic sites, liver metastasis, and PTR were 0.309, 0.496, 0.785, 0.253, and 0.215, respectively. In conclusion, all the results indicated that the PH assumption was satisfied. Cox regression model was used because of PH assumption due to being met. In the Cox regression analysis, only ECOG-PS was found to be an independent prognostic factor associated with overall survival (HR: 0.62, 95% CI: 0.42–0.92, $P = 0.02$) [Table 2].

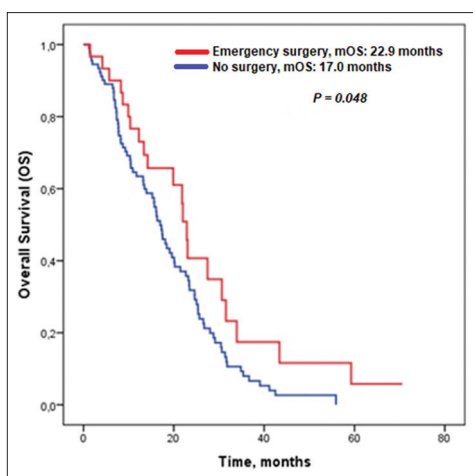


Figure 2: Kaplan–Meier curve for overall survival in emergency surgery and nonsurgical groups

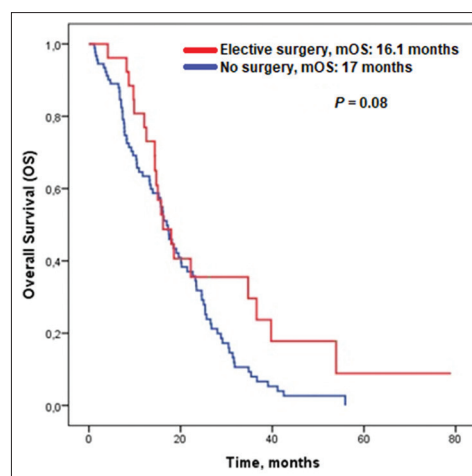


Figure 3: Kaplan–Meier curve for overall survival in elective surgery and nonsurgical groups

DISCUSSION

In this study, emergency or elective resection of primary tumor did not provide a survival advantage in unresectable mCRC patients compared to palliative chemotherapy. Studies in this area are retrospective or secondary analysis of prospective trials and have conflicting results. ESMO, NCCN, and EURECCA guidelines do not recommend PTR in asymptomatic patients with unresectable synchronized Stage IV colorectal cancer.^[13-15] The Cochrane review which is one of the important mainstays of these guidelines and consists analysis of 7 studies showed no benefit of survival in asymptomatic patients with PTR.^[16]

Besides the Cochrane review, there are several studies which did not find any survival benefit of PTR.^[17-19] At the same time, many studies have shown that PTR is associated with high morbidity and mortality rates postoperatively.^[17,20,21] High mortality rates in these studies are usually found in cases taken to the emergency operation.^[20] In our study, morbidity could not be evaluated due to the lack of data. Delayed chemotherapy due to surgical morbidity is another problem in patients undergoing PTR. It is shown that delayed chemotherapy due to surgical morbidity had negative effect on both overall survival and progression-free survival.^[22,23] Because of all these reasons and guidelines, most centers do not perform PTR in asymptomatic patients with unresectable mCRC and start treatment with systemic chemotherapy.

There are several studies in the literature showing that PTR provides a survival advantage.^[24-26] Most of these studies are retrospective cohort studies. Pezold *et al.* analyzed the studies about PTR published between 2010 and 2015 and reported that there have been many limitations in these studies. It has been stated by the authors of the relevant studies that there is insufficient evidence to determine whether PTR is the right approach.^[27,28]

In our study, the median overall survival was numerically longer but statistically insignificant in emergency resection subgroup compared to NS group. This numerical overall survival improvement may be due to the decrease of intestinal complications such as perforation or obstruction. Overall survival was also numerically longer in emergency resection subgroup compared to elective surgery subgroup. This difference may be due to elective surgery-induced delayed chemotherapy.

It is known that right- and left-sided tumors have different clinical and molecular features, and there is strong evidence that tumor localization is a predictive factor for first-line anti-EGFR therapy in metastatic disease. Although there are conflicting data on prognostic effect in the metastatic setting, right-sided colon tumors are considered to have a worse prognosis.^[29,30] In our study, there was a numerical overall survival benefit in the left-sided tumors, but it was not statistically significant (18.4 vs. 16.1 months, respectively; $P = 0.4$). It may be due to small number of patients and retrospective nature of the study. On the other hand, the number of the patients who had right-sided RAS wild tumors and who received first-line anti-EGFR therapy was very limited (two patients). Hence, survival may be different due to the lack of detrimental effects of anti-EGFR therapy in the right-sided tumors.

Relatively small number of patients due to retrospective nature is the primary limitation of our study. Furthermore, we could not make a conclusion about morbidity rates of PTR due to the lack of data. In our study, effect of 14 variables on survival was examined, and statically significant results were evaluated by multivariate analysis which was checked by PH assumption. Unlike other studies, the patients with PTR were evaluated as emergency or elective surgery subgroups and compared with NS group and compared with each other in terms of survival. These

Table 2: Univariate and multivariate analysis of overall survival by categorical

Variable	Median OS (months)	P	Multivariate analysis (HR, 95% CI, P)
Age (years)			
<65	17.4	0.7	-
≥65	19.1		
Sex			
Female	17.5	0.3	-
Male	18.4		
ECOG-PS			
0	22.7	0.004	0.62,
1-2	14.2		0.42-0.92, 0.02
BMI (kg/m ²)			
≥25	19.8	0.1	0.69,
<25	15.7		0.48-1.02, 0.06
Main site of disease			
Rectum	17	0.6	-
Colon	20		
Tumor localization			
Left	18.4	0.4	-
Right	16.1		
Histology			
Adenocarcinoma	19.8	0.5	-
Mucinous carcinoma	17.4		
KRAS			
Mutant	18.5	0.7	-
Wild	16.3		
Number of metastatic sites			
Single	20.2	0.02	0.67,
Multiple	15.6		0.43-1.04, 0.07
Metastatic regions			
Liver (yes/no)	17/24.6	0.1	1.01, 0.61-1.68,
Lung (yes/no)	17.5/20.1	0.9	0.9
Peritoneum (yes/no)	17.5/18.5	0.6	
PTR			
Yes	21.8	0.01	0.65, 0.41-1.02,
No	17		0.06
First-line chemotherapy regimen			
Oxaliplatin based	17.5	0.4	-
Irinotecan based	18.6		
First-line biological agent			
Anti-VEGF agent	18.1	0.8	-
Anti-EGFR agent	19.8		

OS=Overall survival; ECOG-PS=Eastern Cooperative Oncology Group-Performance Score; BMI=Body mass index; HR=Hazard ratio; 95% CI=95% confidence interval; VEGF=Vascular endothelial growth factor; EGFR=Epidermal growth factor receptor; PTR=Primary tumor resection

data were not sufficiently investigated in other studies. These features are the powerful sides of our work that distinguish it from other studies.

CONCLUSION

The role of palliative surgery or local treatments such as endoluminal stent is indisputable in symptomatic patients, but the role of PTR in asymptomatic patients remains

controversial. In our study, it was observed that elective surgery was mostly performed due to incomplete staging. Therefore, preoperative accurate staging should be done. We believe that patients with asymptomatic mCRC should be treated with modern chemotherapy and biological agents until strong evidence is obtained by prospective randomized trials. Thus, the patients can be protected from morbidity and mortality of surgery and loss of time for systemic therapy.

Acknowledgments

This study was approved by our Institutional Ethics Committee and was conducted according to the principles of the Declaration of Helsinki (Decision Date: 18.10.2018, Decision No: 2228/2018).

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Conflicts of interest

There are no conflicts of interest.

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