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Kras-mutation influences outcomes for palliative primary tumor resection in advanced colorectal cancer-a Turkish Oncology Group study

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ABSTRACT

Purpose: We aimed to investigate the prognostic effect of primary tumor resection (PTR) prior to bevacizumab-based treatments in unresectable metastatic colorectal cancer (mCRC).

Methods: We retrospectively collected 341 mCRC cases with unresectable metastases at diagnosis. PTR was performed in 210 cases (the surgery group) and the other patients (n = 131) were followed without PTR (the no-surgery group). All the patients were treated with bevacizumab combined chemotherapy regimens.

Results: The median progression free survival (PFS) of the surgery group was 10.4 months (95% CI: 8.9–11.9), which was significantly better than that of the no-surgery group (7.6 months, 95% CI: 6.4–8.8, $P = 0.000$). The median overall survival (OS) of the surgery group was longer than that of the no-surgery group (27.4 months vs. 18.3 months, respectively, $P = 0.000$). The median PFS and OS of the surgery group were 10.4 months and 28.2 months, which were significantly longer than that of the no-surgery group in Kras-mutant patients (7.8 months and 18.3 months; $P = 0.004$, $P = 0.028$, respectively). There was no difference in terms of PFS and OS between the surgery and the no-surgery groups in Kras-wild type patients.

Conclusion: Palliative PTR may improve the survival outcomes for unresectable mCRC patients. PTR may be preferred, particularly in Kras-mutant patients.

1. Introduction

Colorectal cancer (CRC) is a common type of cancer worldwide [1]. At the time of diagnosis, more than 20% of patients present with metastatic disease [2]. Less than 30% of these patients can be resected curatively. Most of the other patients receive systemic palliative chemotherapy. However, primary tumor resection (PTR) can prevent the complications, such as bleeding, perforation, or obstruction.

Our goal in metastatic colorectal cancer (mCRC) patients is prolonging the survival and improving quality of life. New treatment options, such as irinotecan, oxaliplatin, fluoropyrimidines, VEGF inhibitors and EGFR inhibitors, have provided better response and survival in mCRC.

Furthermore, the impact of PTR in unresectable metastatic CRC (mCRC) patients is inconclusive. Non-curative PTR to prevent local tumor complications, particularly during chemotherapy, were advocated [3–5] in earlier series. Post-operative morbidity and delaying the systemic therapy might be the handicaps in palliative PTR [4,6,7].

In a meta-analyze, the effect of PTR on survival in unresectable mCRC patients was investigated [8]. PTR was independently associated with a better overall survival (OS) in this study.

The addition of bevacizumab to fluoropyrimidine-containing chemotherapy in the first line significantly prolongs OS in previously untreated mCRC patients [9,10]. Toxicities, gastrointestinal hemorrhage, and perforations have been seen in these studies. The location of

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hemorrhage was frequently seen in the entire digestive tract [9]. The incidence of gastrointestinal perforation is approximately 1%–2% with the addition of bevacizumab in the large series [11–13].

Our aim was to investigate the prognostic effect PTR prior to bevacizumab-based treatments in unresectable mCRC.

2. Materials and methods

We retrospectively collected 341 consecutive unresectable mCRC cases, which were treated with first-line bevacizumab based therapies between 2006 and 2015 years, from nine centers of the Turkish Oncology Group (TOG) association in Turkey. Palliative PTR was performed in 210 (61.6% of all patients) cases (Surgery Group). PTR did not perform to 131 (38.4% of all patients) cases (No-Surgery Group). In the surgery group, 177 of the patients received a palliative operation before the onset of bevacizumab, and the other 14 patients received palliative surgery after the onset of bevacizumab-based chemotherapy. We could not find the time PTR in the remaining 19 patients. The entire cohort received bevacizumab combined chemotherapy regimens. A patient who underwent curative metastasectomy and PTR was excluded.

The study was approved by the ethics committee at Necmettin Erbakan University, Meram Faculty of Medicine, and carried out in accordance with the Declaration of Helsinki and all applicable regulations.

Various chemotherapy combinations were used with bevacizumab. Among the 341 mCRC patients, 189 (55.4%) were administered fluoropyrimidine + irinotecan + bevacizumab (FI-bev) combined regimens (FOLFIRI-bev or XELIRI-bev), 135 (39.6%) were administered fluoropyrimidine + oxaliplatin + bevacizumab (FO-bev) combined regimens (FOLFOX-bev or XELOX-bev), and 17 (5%) were administered fluoropyrimidine + bevacizumab (F-bev) combined regimens (FUFA-bev or capecitabine-bev) as a first-line treatment (Table 1). Cetuximab was administered in second- or third-line therapies for 77 (66%) of Kras-wild type patients. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of patients was three or less, and patients had appropriate renal, liver, and hematological functions.

Statistical analysis was performed using SPSS version 20.0 for Windows (SPSS, Chicago, IL). Comparisons of groups for continuous variables were based on the independent samples *t*-test. Both OS and PFS were calculated from the start of the bevacizumab-based regimens. The survival was estimated using the Kaplan–Meier method. The log-rank test was used to compare OS and PFS. Univariate and multivariate Cox proportional hazards models were used to quantify the influence of the considered treatment modalities on survival in the presence of other potentially predictive and prognostic factors. P values of < 0.05 were considered statistically significant. Differences in the occurrence of adverse effects between the two chemotherapy regimens were analyzed using the Chi-square test.

Table 1
The demographic difference between the surgery and no-surgery groups.

Groups Case no (%)	Surgery 210 (61.5%)	No-Surgery 131 (38.5%)	Total 341 (100%)	*P*
Age (years)	58 ± 11	58 ± 11	58 ± 11	
Female	82 (39%)	52 (39.7%)	131 (38.5%)	
Male	128 (61%)	79 (60.3%)	210 (61.5%)	
Duration between diagnosis and bevacizumab onset (days)	46.6 ± 23	30.1 ± 20	40.3 ± 23	0.000
Regimens				
FI-bev	117 (55.7%)	72 (55%)	189 (55.4%)	
XELIRI-bev	*20 (9.5%)*	*11 (8.4%)*	*31 (9.1%)*	
FOLFIRI-bev	*97(46.2%)*	*61(46.6%)*	*158(46.3%)*	
FO-bev	83 (39.5%)	52 (39.7%)	135 (39.6%)	
XELOX-bev	*62 (29.5%)*	*36 (27.5%)*	*98 (28.7%)*	
FOLFOX-bev	*21 (10%)*	*16 (12.2%)*	*37 (10.9%)*	
F-bev	10 (4.8%)	7 (5.3%)	17 (5%)	
F-bev	*4 (1.9%)*	*3 (2.3%)*	*7 (2.1%)*	
Capecitabine-bev	*6 (2.9%)*	*4 (3.1%)*	*10 (2.9%)*	
Kras status n (%)				
Wild	71 (52.2%)	47 (51.1%)	118 (51.8%)	
Mutant	65 (47.8%)	45 (48.9%)	110 (48.2%)	
Location of primary tumor				
Caecum	14 (6.7%)	12 (9.2%)	26 (7.6%)	0.261
Right colon	39 (%18.6)	10 (7.6%)	49 (14.4%)	0.003
Hepatic flexure	7 (3.3%)	0 (0%)	7 (2.1%)	0.032
Transverse colon	5 (2.4%)	6 (4.6%)	11 (3.2%)	0.209
Splenic flexure	4 (1.9%)	3 (2.3%)	7 (2.1%)	0.546
Left colon	24 (11.4%)	8 (6.1%)	32 (9.4%)	0.071
Sigmoid colon	49 (23.3%)	33 (25.2%)	82 (24%)	0.396
Recto-sigmoid colon	9 (4.3%)	12 (9.2%)	21 (6.2%)	0.058
Rectum	56 (26.7%)	46 (35.1%)	102 (29.9%)	0.063
Primary lesions > 1	3 (1.4%)	1 (0.8%)	4 (1.2%)	
Metastases				
Liver	105 (50%)	63 (48.1%)	168 (49.3%)	0.409
Lymph nodes	9 (4.3%)	3 (2.3%)	12 (3.5%)	0.256
Peritoneum	19 (9%)	6 (4.6%)	25 (7.3%)	0.09
Lung	9 (4.3%)	5 (3.8%)	14 (4.1%)	0.535
Bone	1 (0.5%)	2 (1.5%)	3 (0.9%)	0.052
Brain	2 (1%)	0 (0%)	2 (0.6%)	
Multiple organ	64 (30.5%)	52 (39.7%)	116 (34%)	
Local	1 (0.5%)	0 (0%)	1 (0.3%)	
Toxicity				
Gastrointestinal perforation	6 (3.2%)	3 (2.8%)	9 (3%)	0.575
Hemorrhage	15 (7.9%)	9 (8.4%)	24 (8.1%)	0.524
Pulmonary embolism	8 (4.2%)	4 (3.7%)	12 (4.1%)	0.550
Deep vein thrombosis	14 (7.4%)	6 (5.6%)	20 (6.7%)	0.362
Delayed wound healing	7 (3.7%)	2 (1.9%)	9 (3%)	0.303

FI-bev; Fluoropyrimidine-Irinotecanplusbevacizumab, FO-bev; Fluoropyrimidine-Oxaliplatinplusbevacizumab, F-bev; Fluoropyrimidineplusbevacizumab.FOLFIRI-bev; fluorouracil + irinotecan + bevacizumab, XELIRI-bev; capecitabine + irinotecan + bevacizumab, FOLFOX-bev; fluorouracil + oxaliplatin + bevacizumab, XELOX-bev; capecitabine + oxaliplatin + bevacizumab, FUFA-bev; fluorouracil + folinicacit + bevacizumab, capecitabine-bev; capecitabine + bevacizumab.

3. Results

The patient population was comprised of 210 men (61.5%) and 131 women (38.5%). The mean age at diagnosis was 58 ± 11 years (range, 21–84 years; median, 60 years). Primary tumor locations and regions of metastases were shown in Table 1.

Within the median followup of 15.5 months, 172 (50.4%) patients died from their diseases. The median PFS of the surgery group was 10.4 months, which was significantly longer than that in the no-surgery group (7.6 months; $P = 0.000$) (Table 2, Fig. 1). As shown in Fig. 1, the median OS of the surgery group was 27.4 months, which was significantly longer than that in the no-surgery group (18.3 months; $P = 0.000$).

The median PFS and OS of the surgery group that received FI-bev were 11.5 months and 29.4 months, which were significantly longer than that in the no-surgery group (7.4 months and 17.8 months, $P = 0.000$, $P = 0.001$) (Fig. 1). In the surgery group, the PFS of the FI-bev group was significantly better than the FO-bev group and longer than the F-bev group (11.5 months vs. 9 vs. 3.9 months, $P = 0.056$, $P = 0.014$, respectively).

The surgery group had longer PFS (10.4 months vs. 1.8 months) and OS (28.2 months vs. 18.3 months) than the no-surgery group in Kras-mutant patients (HR: 0.52 and 0.52, $P = 0.006$ and 0.028, respectively) (Fig. 2). There was no difference in terms of PFS and OS between the surgery and the no-surgery groups in Kras-wild type patients. PTR and ECOG-PS were the significant prognostic factors in Kras-mutant