JBUON 2019; 24(4): 1494-1500
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Assessment of survival and prognostic factors in metastatic colorectal cancer patients treated with first-line bevacizumab-based therapy

Nazim Can Demircan, Faysal Dane, Mehmet Akif Ozturk, Nalan Akgul Babacan, Mehmet Besiroglu, Serap Kaya, Ozlem Ercelep, Eda Tanrikulu, Suleyman Halil, Sinan Koca, Ozkan Alan, Rahip Hasano, Perran Fulden Yumuk

Marmara University School of Medicine, Department of Internal Medicine, Division of Medical Oncology. Feuzi Cakmak Mah. Muhsin Yazicioglu Cad. No: 10, UST Kaynarca, Pendik, 34890, Istanbul, Turkey.

Summary

Purpose: *Colorectal cancer (CRC) is a significant cause of cancer mortality worldwide. Survival has improved with bevacizumab in metastatic CRC treatment. Our purpose was to analyse survival and prognostic factors in metastatic CRC patients treated with first-line bevacizumab-based treatment.*

Methods: *Files of CRC patients were examined retrospectively and 360 patients treated with first-line bevacizumab were included. Objective response rates (ORRs), median progression-free and overall survival (PFS and OS) of the patients were calculated. Survival was analyzed with the Kaplan-Meier method. Log-rank test and Cox regression model were used for univariate and multivariate analyses, respectively.*

Results: *Median age at diagnosis was 59.5 years. Of the patients 74.4% had initially stage IV disease. Median PFS was 8.5 months, median OS 25.3 months and overall response rate (ORR) 51.4%. ORRs, median PFS and OS of KRAS mutant and wild-type or unknown patients were statistically similar. In left-sided disease, median PFS and OS (9.6 and 27.1 months) were superior compared to right-sided disease (7.3 and 19.4 months) (p=0.005 and 0.02, respectively). Primary disease location, histopathologic grade, primary surgery and metastasectomy affected OS significantly. Histopathologic grade (hazard ratio=1.77, p=0.002) and metastasectomy (hazard ratio=0.48, p=0.001) were independent prognostic factors.*

Conclusions: *Our study confirmed that after bevacizumab-based treatment, KRAS status might not be a prognostic factor. We have also shown that left CRCs have more favorable outcomes than right CRCs in bevacizumab therapy. Additionally, even in metastatic setting histopathologic grade of the primary CRC together with metastasectomy are independent prognostic factors.*

Key words: *bevacizumab, colorectal cancer, prognostic factors*

Introduction

Colorectal cancer (CRC) is a major cause of cancer mortality worldwide. It is the second most frequent cancer in men and the third most frequent cancer in women, while it is the third leading cause of cancer-related mortality [1,2]. It is estimated that over 1.23 million cases are diagnosed and 600.000 associated deaths occur in a year globally [1]. Nearly 30% of CRC patients have metastatic disease at the time of diagnosis and 25-40% of patients treated with curative intent experience recurrence or

Corresponding author: Nazim Can Demircan, MD. Trakya University, Department of Medical Oncology. Sukrupasa Mah. Mithat Vardar Cad. Edirne Plus 62/B No: 19 Edirne, Turkey.
Tel (Work): +90 284 235 76 41-1854, Tel (Mobile): +90 506 947 72 36. Email: ncdemircan@gmail.com
Received: 11/12/2018; Accepted: 15/01/2019

progression [3,4]. The most frequent metastatic site of CRC is the liver, with nearly 25% of patients having liver metastases at the time of diagnosis and about 50% of patients developing liver metastases in 3 years after primary surgery [5].

In the 2000s, the biological agents bevacizumab, cetuximab and panitumumab were approved and since then have been used in metastatic CRC treatment. Phase III trials showed that these agents improved objective response rates (ORRs), progression-free survival (PFS) and overall survival (OS) when added to combined first-line cytotoxic chemotherapy consisting of 5-fluorouracil (5-FU) or capecitabine plus oxaliplatin or irinotecan [6-10]. Bevacizumab is a monoclonal antibody in the form of a humanized immunoglobulin (IgG_1) that inhibits the activity of vascular endothelial growth factor receptor 2 (VEGFR-2). It interrupts the interaction of all isoforms of vascular endothelial growth factor A (VEGF-A) with VEGFR-2, thereby causing microvasculature regression and inhibiting angiogenesis [5]. Two randomised phase III trials showed that in metastatic CRC patients, adding bevacizumab to first-line 5-FU plus irinotecan therapy improved survival rates significantly [9,10].

In our study, we aimed to analyze response rates, survival and prognostic factors in metastatic CRC patients treated with first-line bevacizumab-based therapy.

Methods

Study design and patient selection

In this retrospective and observational study, we reviewed the medical files of 1350 CRC patients diagnosed and followed up between January 1997 and December 2014 in the Medical Oncology Clinic at Marmara University, Pendik Training and Research Hospital. From 385 patients (28.5%) who were initially metastatic and 256 patients (18.9%) who developed metastases or local recurrence later, 360 patients treated with first-line bevacizumab were included in the study. An approval from the ethics committee was granted beforehand.

Demographic data (age at diagnosis and gender), location of the primary tumor, initial disease stage, sites of distant metastasis, Kirsten rat sarcoma viral oncogene (KRAS) mutational status, history of primary surgical operation and metastasectomy were recorded. Pathology reports were also examined for histologic grade and existence of mucinous histology. The cytotoxic chemotherapy regimens administered with bevacizumab, dates of the first therapy cycle and responses to first-line treatment (according to the RECIST criteria) were determined. We also acquired the date of disease progression (according to the RECIST criteria) during or after completion of first-line treatment and date of death or last visit from the medical files of patients.

Table 1. Baseline characteristics of the patients and tumors

Characteristics	*Number of patients (%)*
Gender	
Female	159 (44.2)
Male	201 (55.8)
Age, years	
<60	180 (50)
≥60	180 (50)
Location of primary disease	
Rectum	141 (39.2)
Sigmoid colon	87 (24.2)
Ascending colon and caecum	77 (21.4)
Descending colon	31 (8.6)
Transverse colon	16 (4.4)
Rectosigmoid junction	8 (2.2)
Left side / right side	267 (74.2) / 77 (21.4)
Initial stage	
Stage I	7 (1.9)
Stage II	32 (8.9)
Stage III	46 (12.8)
Stage IV	268 (74.4)
Unknown	7 (1.9)
Primary surgery	
Yes	280 (77.8)
No	80 (22.2)
Histologic grade	
Grade 1	15 (4.2)
Grade 2	169 (46.9)
Grade 3	36 (10)
Grade 4	19 (5.3)
Unknown	121 (33.6)
Mucinous component	
Yes	82 (22.8)
No	149 (41.4)
Unknown	129 (35.8)
KRAS status	
Mutant	125 (34.7)
Wild type	96 (26.7)
Unknown	139 (38.6)
Site of metastasis	
Liver	232 (64.4)
Lung	85 (23.6)
Abdominal lymph nodes	75 (20.8)
Peritoneum	50 (13.9)
Bone	17 (4.7)
Other	56 (15.6)
Metastasectomy	
Yes	63 (17.5)
No	297 (82.5)

Statistics

SPSS version 21.0 software (Armonk, NY, IBM Corp) was used for all statistical analyses. ORR was described as the proportion of patients with partial and complete responses. PFS was defined as the time interval between the start of first-line treatment and disease progression or death or last visit in the absence of progression. OS was accepted as the time interval between the diagnosis of metastatic disease and death or last visit. Analysis of PFS and OS was done with Kaplan-Meier method. Stratified log-rank test was used in univariate analysis to compare survival. Prognostic factors with a p value of <0.05 in univariate analysis were entered in multivariate analysis which was done with Cox regression model and hazard ratio (HR) of each factor calculated. Initial stage and KRAS status were included in the multivariate analysis regardless of their potential of being a prognostic factor. For statistical purposes, initial stage was grouped as metastatic and non-metastatic; primary tumor location as left-sided (from rectum to splenic flexure), right-sided (from caecum to hepatic flexure) and transverse colon; KRAS mutational status as mutant and wild-type or unknown. Confidence interval (CI) was accepted as 95% and p value <0.05 showed statistical significance.

Table 2. Chemotherapy regimens administered in first-line with bevacizumab

Chemotherapy regimens	*Number of patients (%)*
5-FU+LV+irinotecan (FOLFIRI)	176 (48.9)
Capecitabine+oxaliplatin (XELOX)	124 (34.4)
Capecitabine+irinotecan (XELIRI)	19 (5.3)
5-FU+LV+oxaliplatin (FOLFOX)	17 (4.7)
5-FU+LV (FUFA)	12 (3.3)
Capecitabine	7 (1.9)
Irinotecan	5 (1.4)

5-FU: 5-fluorouracil, LV: calcium leucovorin

Results

Patient characteristics

Median age at diagnosis was 59.5 years (52-67). There was a male predominance (55.8%). Left-sided disease prevailed (74.2%) while 77 patients (21.4%) had right-sided primary tumor. Of all patients, 280 (77.8%) were operated for primary tumor. High-grade (grade 3 and 4) histology was detected in 55 patients (15.3%). There was a mucinous component in 82 patients (22.8%). The majority of the patients (74.4%) had initially stage IV disease. Liver was the most frequent site of metastasis (64.4%), while lung was the second leading site (23.6%). In 45 patients (12.5%) local recurrence occurred. KRAS was mutant in 125 patients (34.7%) and wild-type in 96 (26.7%). Metastasectomy was performed in 63 patients (17.5%), with liver being the most frequent site (53 patients). Table 1 summarizes the baseline characteristics of the patients and tumors.

Chemotherapy regimens, response to treatment and progression-free survival

Bevacizumab was administered with capecitabine plus oxaliplatin (XELOX regimen) or 5-FU and calcium leucovorin plus irinotecan (FOLFIRI regimen) mostly (Table 2). A hundred and fifty-three patients (42.5%) had partial response, 57 (15.8%) had stable disease and 32 (8.9%) had complete response, while 84 patients (23.3%) experienced progressive disease. ORR was 51.4% overall. KRAS mutant patients had an ORR of 62.9%, while patients with wild-type or unknown KRAS status had an ORR of 53.3%.

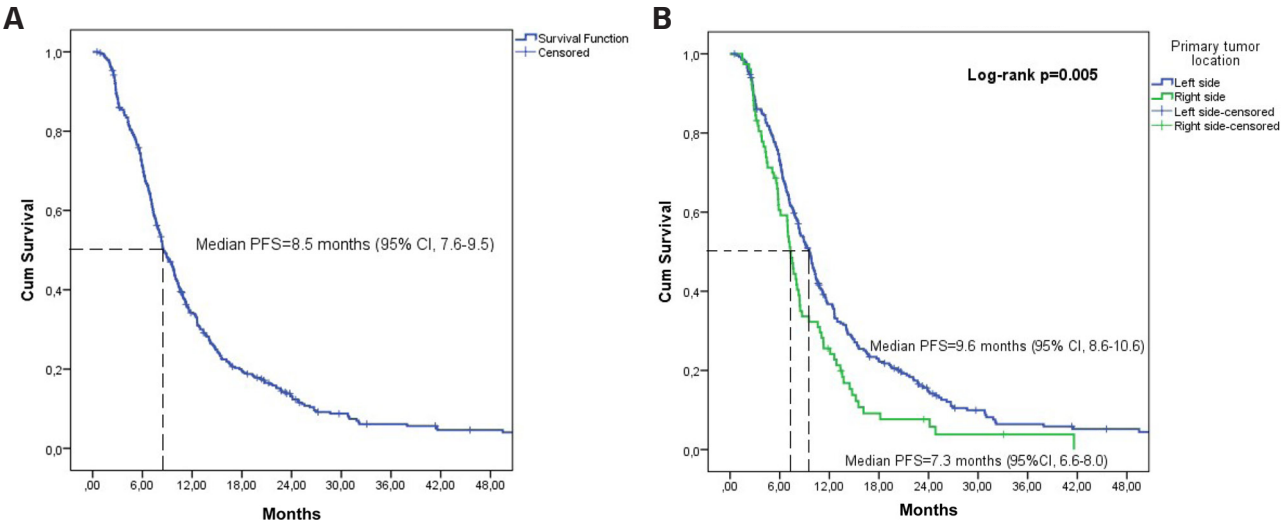

Figure 1. A: Progression-free survival (PFS) stratified by location of the primary tumor. Horizontal and vertical axes show PFS in months and cumulative survival rate, respectively (CI: confidence interval). **B:** Progression-free survival (PFS) stratified by location of the primary tumor. Horizontal and vertical axes show PFS in months and cumulative survival rate, respectively (CI: confidence interval).

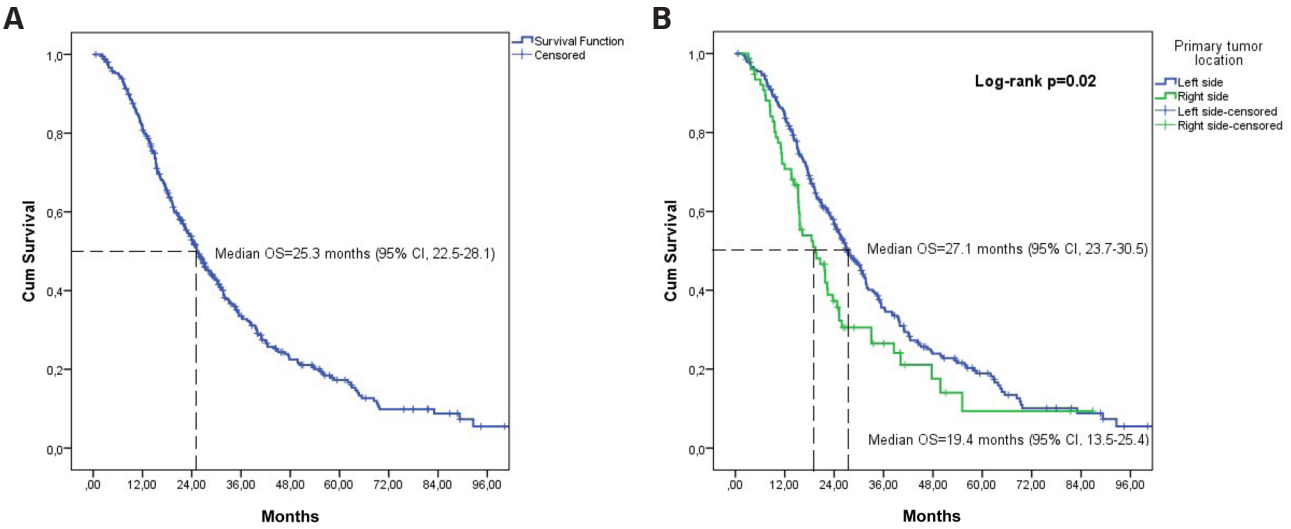

Figure 2. A: Overall survival (OS) of all patients. Horizontal and vertical axes show OS in months and cumulative survival rate, respectively (CI: confidence interval). **B:** Overall survival (OS) stratified by location of the primary tumor. Horizontal and vertical axes show OS in months and cumulative survival rate, respectively (CI: confidence interval).

Table 3. Univariate and multivariate analyses of prognostic factors for overall survival

Factors	*Median OS (months)*	*p value in univariate analysis*	*HR in multivariate analysis (95% CI)*	*p value in multivariate analysis*
Gender		0.18		
Male	26.9			
Female	24.0			
Age, years		0.8		
<60	26.2			
≥60	25.2			
Location of primary		0.02	1.29 (0.85-1.95)	0.24
Left side	27.1			
Right side	19.4			
Initial stage		0.28	1.11 (0.78-1.60)	0.55
Stage I-III	29.0			
Stage IV	25.2			
Histologic grade		<0.001	1.77 (1.24-2.53)	0.002
Low grade (1-2)	34.8			
High grade (3-4)	19.0			
Mucinous component		0.53		
Yes	25.3			
No	31.9			
Primary surgery		<0.001	0.51 (0.25-1.04)	0.06
Yes	29.8			
No	14.8			
Metastasectomy		<0.001	0.48 (0.31-0.73)	0.001
Yes	49.8			
No	22.5			
KRAS status		0.61	0.95 (0.67-1.34)	0.76
Mutant	28.1			
Wild-type or unknown	24.1			

OS: overall survival, HR: hazard ratio, CI: confidence interval

Median PFS was 8.5 months (95% CI, 7.6-9.5) in all patients (Figure 1A). Patients with left-sided disease had a median PFS of 9.6 months (95% CI, 8.6-10.6), while in the group with right-sided disease the median PFS was 7.3 months (95% CI, 6.6-8.0) (p=0.005) (Figure 1B). Patients with mutant KRAS status had a median PFS of 9.5 months (95% CI, 7.9-11.1), whereas patients with wild-type or unknown KRAS status had a median PFS of 8.3 months (95% CI, 7.1-9.5) (p=0.75).

Overall survival and prognostic factors

Median OS was 25.3 months (95% CI, 22.5-28.1) in all patients (Figure 2A). In patients with left- and right-sided disease, the median OS was 27.1 months (95% CI, 23.7-30.5) and 19.4 months (95% CI, 13.5-25.4), respectively (p=0.02, Figure 2B). Patients with mutant KRAS status had a median OS of 28.1 months (95% CI, 22.9-33.3), while patients with wild-type or unknown KRAS had a median OS of 24.1 months (95% CI, 20.6-27.7) (p=0.61). Location of the primary tumor, histologic grade, history of primary surgery and metastasectomy were the prognostic factors for OS. In the Cox regression analysis, higher histologic grade (HR=1.77, p=0.002) and history of metastasectomy (HR=0.48, p=0.001) independently predicted OS. Analysis of prognostic factors is shown in Table 3.

Discussion

Survival of metastatic CRC patients has significantly improved in recent years after the introduction of bevacizumab, the efficacy of which in the first-line setting was demonstrated in various clinical trials [9,10]. However, there are several well-known prognostic factors implicated in CRC. Our study revealed that metastatic CRC patients treated with first-line bevacizumab in addition to cytotoxic chemotherapy had favorable outcomes regardless of KRAS status. Moreover, we determined that among all patients, left-sided CRC had superior PFS and OS compared to right-sided CRC. On the other hand, histologic grade and metastasectomy were independently associated with long-term outcomes.

Location of the primary disease in CRC can affect prognosis. This can be in part explained by the fact that right-sided colon cancers tend to have larger tumor size, poorly differentiated histology and are more frequently associated with BRAF mutation [11,12]. The impact of tumor sidedness on survival was demonstrated in a recent study which showed that left-sided CRC patients treated with bevacizumab had superior PFS and OS to right-sided CRC patients [13]. On the contrary, it was previously shown that in stage I-III CRC, there wasn't a significant difference in mortality between left- and right-sided cancers for all stages combined [14]. Thus, the prognostic value of tumor location seems arguable and further studies are necessary at least for early stage CRC. Our study supports the findings that left-sided CRC has favorable outcomes with first-line bevacizumab treatment. However, not being an independent prognostic factor after adjusting for other factors, emphasizes that disease location has a low prognostic value in CRC.

The KRAS proto-oncogene is mutated in approximately 35-45% of CRCs [15]. In metastatic CRC, it is performed as a routine test and determines treatment decisions. Some of the previous studies suggest that KRAS mutations in CRC are associated with poor prognosis, while other studies imply that they are not of prognostic value [16-18]. For instance, the prognostic value of KRAS status could not be confirmed in both early and advanced disease stage in a study which included 1096 CRC patients of whom 401 had KRAS mutation [19]. According to other studies, KRAS mutations are neither predictive nor prognostic in CRC patients receiving anti-VEGF therapy and bevacizumab is effective independent of KRAS status [20,21]. These findings may support the thought that KRAS mutations are rather predictive for the inefficacy of anti-EGFR therapy, which was not evaluated here. In our study, KRAS mutant patients had a better median OS (28.1 vs. 24.1 months), but this did not turn into a statistical superiority either (p=0.61). Additionally, patients with mutant or wild type KRAS status had similar ORRs and PFS, further reflecting the efficacy of bevacizumab in both groups.

The initial stage is one of the most important factors that determines the course of CRC, especially in the postoperative period [22]. Literature data are currently inadequate to compare long-term outcomes of bevacizumab-receiving CRC patients who were initially metastatic or initially at early-stage but relapsed later. The OS advantage of initially early-stage patients (3.8 months) did not reach statistical significance in our analysis (p=0.28). This may be attributed to the rather low number of patient in both groups and also the imbalance between their sizes. In addition to the initial stage, histologic grade reflects tumor differentiation and it is clearly of prognostic value independent of stage [23]. Our findings are in line with this, showing that patients with high grade histology had worse OS and it was independently associated with approximately 1.8-fold increased risk of death. Beside intracellular mucin production which can lead to signet ring cell carcinoma and is

associated with a poor prognosis in CRC, it is debated whether extracellular mucinous component is a prognostic factor or not [24]. In our study, it was not a significant predictor of survival despite an OS difference of 6.6 months (p=0.53). This may be associated with the underrepresentation of cases with mucinous component and unavailability of information about it in nearly 36% of the patients.

Operation of the primary tumor in metastatic CRC is controversial, but literature data suggests that it could be a favorable prognostic factor [25]. Several studies are comparing OS of metastatic CRC patients with primary tumor resection (PTR) and intact primary tumor. One of them reported that the median OS was 27.4 months in operated patients while it was 18.3 months in the no-surgery group, and this showed a high statistical significance [26]. Other studies also highlight the significant survival advantage in PTR patients, with a median OS up to 30.7 months [27]. In our study, the majority of patients had stage IV initially, and most of them had PTR. Median OS of patients with PTR was 29.8 months, showing proximity to the values mentioned above. Despite providing a 49% risk reduction for death, PTR was not an independent prognostic factor but had a trend toward statistical significance (p=0.06). The heterogeneity of our patients can elucidate this because a portion of them was in early-stage in the time of diagnosis and primary surgery, which may have confounded the evaluation of PTR as a prognostic indicator in metastatic CRC.

In CRC with limited metastases (especially in the liver and the lungs) metastasectomy can improve long-term outcomes, with a 5-year overall survival up to 58% [28]. It may be particularly unsuitable to numerically compare the median OS (49.8 months) of 63 metastasectomy patients in our study with literature because it encompasses various metastatic sites that were operated. Nevertheless, this study indicates that patients with metastasectomy have a statistically significant improvement in OS and a 52% decrease in the risk of death. Therefore, we suggest that all patients with favorable response to bevacizumab therapy should be evaluated for metastasectomy.

The impact of age on the prognosis of CRC is controversial, and many studies have shown no significant difference between younger and older patients [29]. We determined that OS in patients younger than 60 years and 60 years or older was similar. Gender also was not a significant prognostic factor in many studies [30]. Likewise, female and male patients had comparable OS in our analysis.

Due to the nature of this study, it has all the handicaps of retrospective studies such as selection or observation biases. Patients were heterogeneous in some features, and data were collected incompletely. We did not evaluate the contribution of second or later lines of therapies. Also, in a remarkable portion of the patients, even KRAS status was unknown. Moreover, NRAS and BRAF status, which are of prognostic value but were not included in our study, could be further confounding. Patients were not tested for these parameters since at the time of treatment, these tests were not evaluated routinely in daily practice.

In conclusion, this study has shown that KRAS status may not have prognostic importance in metastatic CRC patients treated with bevacizumab. Our study also confirmed that left colon cancers have more favorable outcomes than right colon cancers in a relatively small group of metastatic CRC patients. Finally, even in metastatic CRC patients treated with biological agents, the histopathologic grade of the primary tumor and metastasectomy continue to be independent prognostic factors.

Acknowledgements

The authors would like to thank Dr. Osman Kostek for help in editing the manuscript.

Conflict of interests

The authors declare no conflict of interests.

References

1. Gill S, Dowden S, Colwell B, Collins LL, Berry S. Navigating later lines of treatment for advanced colorectal cancer – Optimizing targeted biological therapies to improve outcomes. Cancer Treat Rev 2014;40:1171-81.
2. Goldstein DA, Zeichner SB, Bartnik CM, Neustadter E, Flowers CR. Metastatic colorectal cancer: A systematic review of the value of current therapies. Clin Colorectal Cancer 2016;15:1-6.
3. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 2007;50:1783-99.
4. Scholefield JH, Steele RJ. Guidelines for follow up after resection of colorectal cancer. Gut 2002;51(Suppl 5):V3-5.
5. Van Schaeybroeck S, Lawler M, Johnston B et al. Colorectal cancer. In: Niederhuber JE, Armitage JO, Doro-

show JH, Kastan MB, Tepper JE (Eds): Abeloff's Clinical Oncology (5th Edn). Elsevier, Philadelphia, 2014, p1319, p1322, p1327, p1329, p1330, p1332.

6. Van Cutsem E, Lang I, Folprecht G et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial. Presented at the 2010 Gastrointestinal Cancers Symposium, Orlando, USA, 22-1-2010. Abstract no. 281.
7. Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-14.
8. Douillard JY, Siena S, Cassidy J et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 2014;25:1346-55.
9. Peeters M, Price T. Biologic therapies in the metastatic colorectal cancer treatment continuum – Applying current evidence to clinical practice. Cancer Treatment Rev 2012;38:397-406.
10. Fuchs CS, Marshall J, Mitchell E et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-86.
11. Gao XH, Yu GY, Gong HF et al. Differences of protein expression profiles, KRAS and BRAF mutation, and prognosis in right-sided colon, left-sided colon and rectal cancer. Sci Rep 2017;7:7882.
12. Sinicrope FA, Mahoney MR, Smyrk TC et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. J Clin Oncol 2013;31:3664-72.
13. Venook AP, Niedzwiecki D, Innocenti F et al. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34 (Suppl):Abstract no. 3504.
14. Weiss JM, Pfau PR, O'Connor ES et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results-Medicare data. J Clin Oncol 2011;29:4401-9.
15. Tan C, Du X. KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol 2012;18:5171-80.
16. Tanaka M, Omura K, Watanabe Y, Oda Y, Nakanishi I. Prognostic factors of colorectal-cancer - k-ras mutation, overexpression of the P53-protein, and cell proliferative activity. J Surg Oncol 1994;57:57-64.
17. Andreyev HJ, Norman AR, Cunningham D, Oates JR, Clarke PA. Kirsten ras mutations in patients with colorectal cancer: The multicenter "RASCAL" study. J Natl Cancer Inst 1998;90:675-84.
18. Dix BR, Robbins P, Soong R, Jenner D, House AK, Iacopetta BJ. The common molecular genetic alterations in Dukes' B and C colorectal carcinomas are not short-term prognostic indicators of survival. Int J Cancer 1994;59:747-51.
19. Won DD, Lee JI, Lee IK, Oh S, Jung ES, Lee SH. The prognostic significance of KRAS and BRAF mutation status in Korean colorectal cancer patients. BMC Cancer 2017;17:403.
20. Hurwitz HI, Yi J, Ince W, Novotny WF, Rosen O. The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer. Oncologist 2009;14:22-8.
21. Kim ST, Park KH, Shin SW, Kim YH. Dose KRAS mutation status affect on the effect of VEGF therapy in metastatic colon cancer patients? Cancer Res Treat 2014;46:48-54.
22. Edge SB, Byrd DR, Compton CC et al (Eds). AJCC (American Joint Committee on Cancer) Cancer Staging Manual (7th Edn). Springer, New York, 2010, p133.
23. Griffin MR, Bergstralh EJ, Coffey RJ et al. Predictors of survival after curative resection of carcinoma of the colon and rectum. Cancer 1987; 60:2318.
24. Hyngstrom JR, Hu CY, Xing Y et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol 2012;19:2814.
25. Verhoe C, De Wilt JH, Burger JWA, Verheu HMW, Koopman K. Surgery of the primary in stage IV colorectal cancer with unresectable metastases. Eur J Cancer 2011;47 (Suppl 3):61-6.
26. Korkmaz L, Coskun HS, Dane F et al. Kras-mutation influences outcomes for palliative primary tumor resection in advanced colorectal cancer-a Turkish Oncology Group study. Surg Oncol 2018;27:485-9.
27. De Mestier L, Manceau G, Neuzillet C et al. Primary tumor resection in colorectal cancer with unresectable synchronous metastases: A review. World J Gastrointest Oncol 2014;6:156-69.
28. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. World J Gastroenterol 2011;17:4067-75.
29. Alici S, Aykan NF, Sakar B, Bulutlar G, Kaytan E, Topuz E. Colorectal cancer in young patients: characteristics and outcome. Tohoku J Exp Med 2003;199:85-93.
30. Nelson RL, Dollear T, Freels S, Persky V. The relation of age, race, and gender to the subsite location of colorectal carcinoma. Cancer 1998;82:1408-10.