JBUON 2020; 25(1): 212-219
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Survival of patients with liver metastases from colorectal cancer treated with bevacizumab and FOLFOX4

Miljana Dzunic[1], Marija Andjelkovic-Apostolovic[2,3], Svetislav Vrbic[1,3], Ivica Pejcic[1,3], Ivan Petkovic[1,3], Ana Cvetanovic[1,3], Sasa Dinic[1]

[1]Clinic of Oncology, Clinical Center Nis, Nis, Serbia; [2]Public Health Institute in Nis, Nis, Serbia; [3]Medical Faculty, University of Nis, Nis, Serbia.

Summary

Purpose: *In patients with colorectal liver metastases (CLM) a long term survival and the probability of cure might be achieved through the surgical treatment of metastatic sites after prior application of systemic treatment. The purpose of this study was to assess the survival of patients with unresectable CLM treated with bevacizumab (bev) and FOLFOX4 (FOLFOX-bev) and to compare survival according to patient, disease and treatment characteristics.*

Methods: *This research included 110 patients with unresectable CLM treated with FOLFOX-bev. Treatment response and resectability were estimated every 3 months. If resectability was achieved, patients were operated on and followed. Patient, disease and treatment characteristics in patients with and without hepatectomy were compared. Survival was estimated according to Kaplan-Meier method. Comparison of survival according to patient, disease and treatment characteristics was performed using log-rank test.*

Results: *In patients with hepatectomy, treatment response was significantly more frequent (63, 63% vs 16, 66%, p<0.001). One- and three-year survival rate for the whole group was 87, 3% and 36, 1%, respectively; median overall survival (OS) was 23 months (95%CI 19, 63-28, 26). One- and three-year survival for patients with hepatectomy was 98, 48%, and 54, 76%, respectively; median OS was 35 months (95%CI 28, 83-41, 17). Three-year survival was significantly better in patients with hepatectomy (HR=3.775; 95%CI 2.150-6.627, p<0.001), older than 60 years (p=0.033), those without extrahepatic metastases (p=0.008) and those with treatment response (p=0.05).*

Conclusion: *Significantly better survival had patients with hepatectomy, treatment response, older than 60 years and without extrahepatic metastases. FOLFOX4-bev is effective treatment for molecularly unselected patients.*

Key words: *bevacizumab, colorectal cancer, hepatectomy, liver metastases, survival*

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer morbidity and mortality worldwide [1]. In Europe, this is the second most common cancer and the second cause of cancer-related deaths, with about 500,000 new cases and 243,000 deaths in 2018 [2]. Nearly three quarters of patients will have metastatic colorectal cancer (mCRC), diagnosed either initially or during the disease course [3]. mCRC is commonly treated with palliative chemotherapy and linked with poor prognosis [4]. However, in patients with metastases confined to the liver, a long term survival and probability of cure might be achieved with the surgical treatment of metastatic sites [5,6].

Although about 20-30% of mCRC patients have liver-limited metastases, for the majority of them liver resection with curative intent is not possible unless chemotherapy is used [7,8]. The aim of ap-

Corresponding author: Miljana Dzunic, MD. Dr Zoran Djindjic Boulevard 48, 18000 Nis, Serbia.
Tel: +381 69 217 16 33, Fax: +381 18 4233 967, Email: drmdzunic@gmail.com
Received: 28/02/2019; Accepted: 07/04/2019

plied systemic therapy is to provide optimal downstaging in order to make liver surgery feasible and complete (R0 resection) and to deal with eventual micrometastatic foci that remained undetected. When resection of colorectal liver metastases (CLM) is upfront technically feasible but negative prognostic features are present, systemic treatment prior to liver surgery is also required in order to achieve the best possible outcome [9,10].

A combination of oxaliplatin, leucovorin and 5-fluorouracil given as a bolus and continuous intravenous infusion and bevacizumab (FOLFOX-bev) has been well accepted and effective as a first line regimen for mCRC. The aim of this study was to assess the survival of mCRC patients with CLM initially not suitable for resection who were treated with FOLFOX-bev and to compare the survival according to patient, disease and treatment characteristics.

Methods

Patients

Patients with CLM that were unsuitable for upfront resection (potentially resectable or unresectable), treated with FOLFOX-bev in the Clinic of Oncology, Clinical Center Nis, Serbia, from January 2010 to June 2017 were included.

Inclusion criteria: age ≥18 years, ECOG performance status 0-1, histologically verified colorectal adenocarcinoma and contrast enchanced MSCT-proven unresectable metastases limited to the liver or liver and other organs that were resectable or already ressected (ovary, lungs, small bowel, omentum and peritoneum). Potential resectability was defined after MSCT scan analysis by an experienced hepatobiliary surgical team. The criteria for unresectability were: not possible upfront R0/R1 resection of all hepatic lesions, <30% estimated residual liver volume after resection or metastases in contact with major vessels of the remaining liver. The total number of patients included in the study was 110.

Therapy and assessment

After assessing complete blod count and biochemical analysis, urinalysis, ECG and echocardiography, all patients started FOLFOX4 chemotherapy (oxaliplatin 85 mg/m^{2}on day 1, leucovorin 200 mg/m^2, 5-FU 400 mg/m^2 bolus and 600 mg/m^2 22-hour continuous intravenous infusion on days 1 and 2, repeated every 2 weeks) and bevacizumab (5mg/kg, repeated every 2 weeks).

Response evaluation according to Response Evaluation Criteria in Solid Tumours (RECIST v.1.1) and resectability were assessed using contrast enhanced MSCT scan every three months (after 5 cycles). Patients whose metastases became resectable were operated on 6 weeks after the last chemotherapy and closely followed afterwards (clinical examination, laboratory analyses, tumor marker CEA and abdominal echosonography every 3 months and contrast enhanced MSCT scan that was done postoperatively (at least 4 weeks after hepatectomy) and every 6 months afterwards). Upon progression, patients were treated with available systemic and loco-regional procedures where appropriate.

Data

Age, sex, comorbidities, location of the primary tumor, number of liver metastases, synchronous (within 3 months of primary tumor surgery) or metachronous (more than 3 months after primary tumor surgery), liver involvement, time from the surgery of primary tumor to appearance of liver metastases for metachronous liver involvement, number of FOLFOX–bev chemotherapy cycles, response to chemotherapy, resectablity, type of liver surgery and histopathologic analysis of resected metastatic liver, disease free survival (DFS - time from liver surgery to documented disease progression), the total number of systemic therapy lines, the total number of surgical interventions and local ablative procedures and overall survival (OS– number of months from CLM diagnosis to death) were collected.

Response rate to FOLFOX-bev regimen and resectability were calculated. Patient, disease and treatment characteristics in patients with and without hepatectomy were compared. Survival of all patients and comparison of survival according to age, gender, primary tumor localization, timing of liver metastases, number of metastases, extrahepatic disease presence, treatment response and hepatectomy were performed.

Statistics

Statistical analyses were performed using SPSS statistical software, version 16.0 for Windows. Descriptive statistics were used for qualitative and quantitative assessment of the results: absolute numbers, relative numbers (%), mean value ( ), standard deviation (SD), and median value. Independent two-sided t-test, nonparametric Mann-Whitney U test and chi-square (x^2) test were applied to compare variables between the groups, where appropriate. Survival was estimated using the Kaplan-Meier method. Survival curves were compared using the log-rank test. P values <0.05 were considered statistically significant.

Results

Patients

From 110 patients, 75 (68.2%) were men and 35 (31.8%) women. The average age of patients was 60.81±9.47 years, the youngest being 28 and the oldest 81 years old. Men were significantly older than women (62.22±9.14 vs 57.80±9.58; p=0.022). The most frequent comorbidity was arterial hypertension (27, 27%) and diabetes type 2 (8.18%). A history of malignancy other than CRC had 4 (54%) patients.

Disease characteristics

There was no statistically significant difference in the localization of primary tumor (p=0.209). The

number of patients with synchronous metastases was significantly higher than with metachronous metastases (60.9% vs 39.1%, p=0.022). The mean time to appearance of metachronous disease was 19.23±16.57 months. The average number of liver metastases was 2.90±1.49; Table 1). Multiple liver metastases (≥5) had 40 patients (36.36%). Resected/resectable metastases in organs other than liver were present in 19 patients (17.27%) (Table 1).

Treatment

The average number of received FOLFOX4+bev chemotherapy cycles was 5.76±2.05. Complete response (CR) was documented in 8 patients (7.4%) and 61 patients (56.48%) had partial response (PR). Response rate was 63.88%. The most frequent type of response was PR, and the most uncommon CR, which was statistically significant (p<0.001). Stable disease (SD) was documented in 13 patients (12.03%) and progression (PD) in 26 (24.07%). Liver resection rate was 61.1% (Table 1). R0 hepatectomy was performed in 61 patients (92.42%) and R1 resection was verified in 5 patients (7.57%). Postoperative chemotherapy received 25 patients (37.88%). Median DFS for the group with CLM resection was 8 months (95%CI 9.05-15.55). In 52 from 66 patients (78.79%) recurrence was documented.

Table 1. Disease characteristics and treatment modalities

Characteristics and modalities	*n (%) / mean±SD*	x^2	*p*
Localization of primary tumor		3.127	0.209
Left colon	28 (25.5)		
Right colon	40 (36.4)		
Rectum	42 (38.2)		
Liver metastases		5.236	0.022
Synchronous	67 (60.9)		
Metachronous	43 (39.1)		
Time to appearance of metachronous liver metastases	19.23±16.57		
Number of liver metastases	2.90±1.49		
Other metastatic sites	19 (17.27)		
Number of FOLFOX4+bev cycles	5.76±2.05		
Therapy response (RECIST)		52.455	<0.001
CR	8 (7.4)		
PR	61 (56.48)		
SD	13 (12.03)		
PD	26 (24.07)		
Liver resection	66 (61.1)		
Surgical procedures			
Metastasectomy	48 (72.72)		
Segmentectomy	28 (42.42)		
Lobectomy	6 (9.09)		
Two-stage hepatectomy	3 (4.54)		
Simultaneous operation of primary tumor and liver metastases	7 (10.6)		
Local ablative procedures			
Sclerosation	2 (1.81)		
RFA	2 (1.81)		
Palliative radiotherapy	6 (5.45)		
Number surgical resections			
1	59 (53.63)		
>1	12 (10.9)		
Total number of chemotherapy lines			
1	22 (20)		
2	32 (29.09)		
3	43 (39.09)		
4	8 (7.27)		
5	5 (4.54)		

Table 2. Patient, disease and treatment characteristics according to hepatectomy

Characteristics	*Hepatectomy*		x^2 / *Z	*p*
	Yes *n(%)*	*No* *n (%)*		
Gender			0.698	0.403
Men	47 (71.2)	28 (63.6)		
Women	19 (28.8)	16 (36.4)		
Age, mean±SD	61.09±9.75	60.41±9.11	0.396	0.713
Localization of primary tumor			4.251	0.119
Left colon	14 (21.2)	14 (31.8)		
Right colon	29 (43.9)	11 (25.0)		
Rectum	23 (34.8)	19 (43.2)		
Liver metastases			0.102	0.750
Synchronous	41 (62.1)	26 (59.1)		
Metachronous	25 (37.8)	18 (40.9)		
Time to appearance of metachronous liver metastases, mean±SD	17.84±12.70	21.17±21.06	0.284*	0.776
Number of liver metastases, mean±SD	3.18±1.46	3.54±1.49	1.229*	0.219
Number of FOLFOX4-bev cycles, mean±SD	6.03±2.11	5.36±1.92	1.661*	0.097
Response to therapy (CR+PR)	42 (63.63)	7 (16.66)	22.845	<0.001

* Mann-Whitney U test

Table 3. Three-year survival according to patient, disease and treatment characteristics

Characteristics	$\bar{x}$	*SE*	*95%CI*	*Log rank test*	*p*
Gender				0.090	0.765
Men	24.32	1.39	26.61-27.04		
Women	24.69	2.28	14.97-29.16		
Age, years				4.525	0.033
≤60	20.69	1.386	17.00-24.31		
>60	27.71	1.35	25.05-30.36		
Localization of primary tumor				1.517	0.468
Right colon	21.72	2.36	17.09-26.36		
Left colon	25.89	1.95	22.05-29.73		
Rectum	25.06	1.87	21.28-28.76		
Number of liver metastases				2.993	0.084
1-4	26.25	1.57	23.17-29.34		
≥5	21.88	1.73	18.49-25.28		
Appearance of liver metastases				0.075	0.784
Synchronous	24.57	1.43	21.78-27.37		
Metachronous	24.18	2.15	19.96-28.40		
Extrahepatic metastases				7.074	0.008
No	25.50	1.31	22.93-28.06		
Yes	18.25	2.08	14.18-22.32		
Response to therapy				7.871	0.005
CR+PR	29.75	1.36	23.102-32.49		
SD+PD	21.83	1.52	18.85-24.81		
Hepatectomy				25.143	<0.001
Yes	30.26	1.31	27.69-32.83		
No	18.16	1.63	14.97-21.35		

SE: standard error

There were no statistically significant differences in gender, age, primary tumor localization, synchronous/metachronous liver metastases, time to appearance of metachronous metastases, number of liver metastases and the number of preoperative chemotherapy cycles administered between patients with and without liver resection. Response to therapy was significantly more frequent in patients with hepatectomy (63.63% vs 16.66%, p<0.001) (Table 2).

Survival

One- and three- year survival rate for the whole patient cohort was 87.3% and 36.1%, respectively. Median OS of patients with CLM treated with FOLFOX-bev was 23 months (95%CI 19.63-28.26).

One- and three- year survival for patients with hepatectomy after chemotherapy were 98.48%, and 54.76%, respectively. One- and three- year survival for patients without hepatectomy were 65.9% and 15.79%, respectively. Patients in which liver surgery was done had median OS of 35 months (95%CI 28.83-41.17) and in patients without liver resection the median OS was 15 months (95%CI 13.37-16.63). Three-year survival was significantly better in patients with hepatectomy (HR=3,775, 95%CI 2.150-6.627, p<0.001) (Table 3, Figure 1).

Three-year survival was significantly better in patients older than 60 years (p=0.033) (Table 3, Figure 2), in patients without extrahepatic metastases (p=0.008) (Table 3, Figure 3) as well as in patients with documented response to treatment (CR and PR) (p=0.005, Table 3, Figure 4).

There were no statistically significant differences in three-year survival according to gender (p=0.765), localization of primary tumor (p=0.468), appearance of primary metastases (synchronous/metachronous) (p=0.784) as well as number of liver metastases (p=0.084) (Table 3).

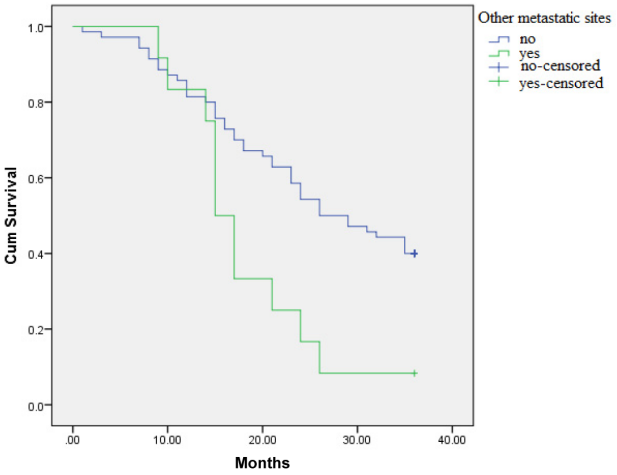

Figure 3. Kaplan-Meier curves of three-year survival according to other metastatic sites (p=0.008).

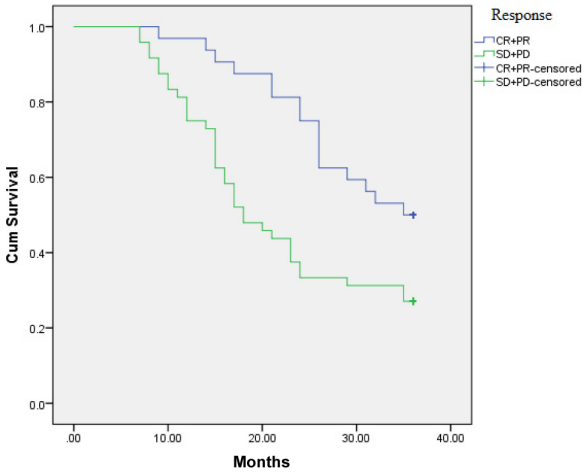

Figure 4. Kaplan-Meier curves of three–year survival according to response to therapy (p=0.005).

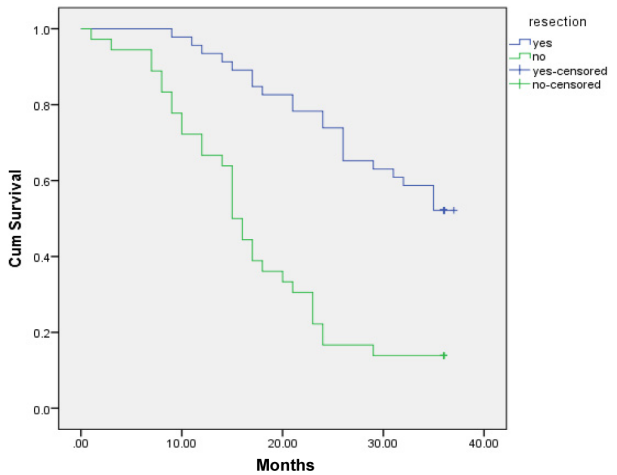

Figure 1. Kaplan-Meier curves of three-year survival according to hepatectomy (p<0.001).

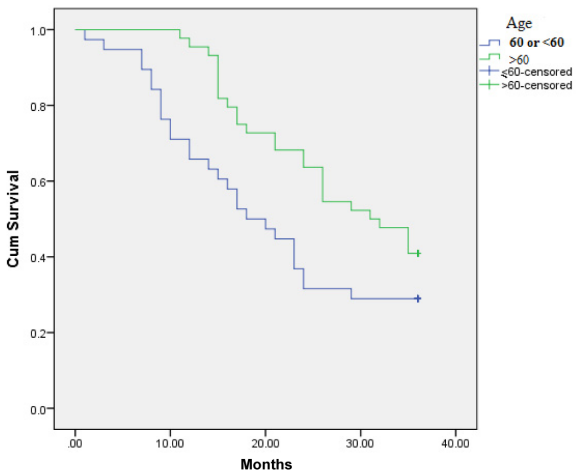

Figure 2. Kaplan-Meier curves of three-year survival according to age (p=0.033).

Discussion

Several studies have reported excellent long-term survival rates after hepatic resection following induction chemotherapy in patients with unresectable CLM [11-15]. Since the resection rates strongly correlate with the response to preoperative treatment [16], for the systemic treatment of unresectable CLM the most efficient regimens should be used. Although the addition of bevacizumab to FOLFOX chemotherapy has not demonstrated improvement in response rate, there are findings to support the use of FOLFOX-bev in the preoperative treatment of CLM. Bevacizumab has shown to improve pathological response, which is found to correlate with patient outcomes [17,18]. Furthermore, it prevents a "blue liver syndrome", liver injury caused by sinusoidal obstruction from oxaliplatin chemotherapy [17], associated with higher complication rates of major hepatectomy, early recurrence and poorer long-term survival after surgical treatment of CLM [19,20]. Bevacizumab improved DFS after hepatectomy [21], proving its utility in the preoperative treatment of CLM.

Similarly to other reported studies [22-26], in our research FOLFOX-bev regimen yielded a response rate of 63.88%. In the OLIVIA trial [24], resection rate after mFOLFOX6-bev was 49%, with R0 resection of 23%. In TRICC0808 study [25], mFOLFOX6-bev provided hepatectomy in 53.3% of patients and R0 resection in 44, and 4%. Both mentioned multicenter prospective trials were performed in patients with clearly unresectable, massive liver disease. In our patient group, 36.36% of patients had multiple liver involvement (≥5 metastases) and the average number of metastases was 2.90±1.49. This explains the higher resection rate in our study (61.1%). Our results showed that response to therapy was significantly more frequent in patients with hepatectomy (63.63% vs 16.16%, p<0.001), stressing the importance of therapeutic regimen effectiveness for achieving resectability. In the study of Beppu et al, responders to chemo and targeted therapy were identified as independent predictive factors for conversion hepatectomy, as well as left-sided colon or rectal cancer, H1/H2 metastases and the absence of extrahepatic metastases [27]. However, significant difference in the primary tumor localization and the number of metastases between patients with and without liver resection in our research has not been found.

According to guidelines, for the initially unresectable CLM, doublet chemotherapeutic combinations with bevacizumab or cetuximab, as well as triplet consisting of fluorouracil, oxaliplatin and irinotecan in combination with bevacizumab (FOLFOXIRI-bev) are preferred [10]. A recent meta-analysis of trials using FOLFOXIRI-bev reported an overall objective response rate of 69%, and R0 resection rates of 62.2% and 54.7% for the subgroup of liver-limited disease [28]. There are data which prove superiority of FOLFOXIRI-bev in direct comparison with mFOLFOX6-bev regimen [24]. However, the toxicity of triplet combination is substantial, and potentially harmful to older and fragile patients. Cetuximab combined with FOLFOX/FOLFIRI regimens provided better response rates in patients with unresectable CLM in RAS wild type subpopulation [29]. In KRAS non-mutant patients cetuximab-mFOLFOX6 showed significantly better response and resection rates compared to mFOLFOX-bev [30], providing the rationale for the use of combined targeted and chemotherapy according to RAS status [31].

Hepatectomy and overall response have been defined as independent prognostic factors in patients with CLM [27,32]. The main parameter which affected survival of our patients was hepatectomy. The median OS of 35 months (95%CI 28.83-41, 17) in patients with resected CLM was significantly better than 15 months (95%CI 13.37-16.63) in non resectable patients (HR=3.775, 95%CI 2.150-6.627, p<0.001); three-year overall survival rate was 54.76% for the patients with hepatectomy vs 15.79% without hepatectomy. The reported median survival in patients with hepatectomy after mFOLFOX-bev of 43.1-month and three-year OS rate of 61.3% [15] might actually be comparable with our results, if we have in mind the humble resources of our healthcare system and problems with drug access that definitely affect patient survival. Similar to aforementioned studies, in our study response to treatment has also reflected in significantly better OS (29.75 vs 21.83 months; p=0.005), as well as the absence of extrahepatic metastases (25.5 vs 18.25 months; p=0.008).

Age is a significant predictor of OS in the mCRC patients, with the youngest and oldest patients showing worse survival than patients of middle age [33]. Survival rates of patients after hepatic resection of CLM tend to be lower in younger (<40 years) compared to the older patients; young patients have more recurrences and significantly lower PFS than elderly [34]. Our results showed better survival of patients older than 60 years than that of younger patients (27.71 vs 20.69 months, p=0.033). It seems that young patients have aggressive and more advanced disease forms and higher number of risk factors, which negatively affect survival. The results suggest a possible value of more intensive systemic treatment approach for the young patients in order to improve their survival.

In the treatment of patients with CLM, preoperative therapy is of the most importance, since it enables complete resection and improves survival. Selection of patients with liver-limited disease and administering intensive chemotherapeutic regimens in combination with targeted therapy for conversion might improve outcome, especially in young patients. However, hepatectomy has proved to be crucial for long-term survival in metastatic colorectal liver disease. To conclude, FOLFOX4-bev regimen is an effective preoperative treatment option, particularly for molecularly non selected and older patient population. Significantly better survival in patients with CLM was observed in patients with hepatectomy, patients with objective response to treatment, patients without extrahepatic metastases and patients older than 60 years.

Conflict of interests

The authors declare no conflict of interests.

References

1. Fitzmaurice C, Akinyemiju TF, Al Lami FH et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2018;4:1553-68.
2. Ferlay J, Colombet M, Soerjomataram I et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-87.
3. Van Cutsem E, Cervantes A, Nordlinger B et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25:iii1-iii9.
4. Siegel RL, Miller KD, Fedewa SA et al. Colorectal cancer statistics. Cancer 2017;67:177-93.
5. Choti MA, Sitzmann JV, Tiburi MF et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
6. Weiser MR, Jarnagin WR, Saltz LB. Colorectal cancer patients with oligometastatic liver disease: what is the optimal approach? Oncology (Williston Park) 2013;27:1074-8.
7. Garden OJ, Rees M, Poston GJ et al. Guidelines for resection of colorectal cancer liver metastases. Gut 2006;55:iii1-iii8.
8. Maeda Y, Shinohara T, Nagatsu A, Futakawa N, Hamada T. Long-term outcomes of conversion hepatectomy for initially unresectable colorectal liver metastases. Ann Surg Oncol 2016;23:S242-8.
9. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.
10. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-1422.
11. Adam R, Delvart V, Pascal G et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. Ann Surg 2004;240:644-57.
12. Masi G, Loupakis F, Pollina L et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Ann Surg 2009;249:420-5.
13. Adam R, Wicherts DA, de Haas RJ et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009;27:1829-35.
14. Lam VW, Spiro C, Laurence JM et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. Ann Surg Oncol 2012;19:1292-1301.
15. Yasuno M, Uetake H, Ishiguro M et al. mFOLFOX6 plus bevacizumab to treat liver-only metastases of colorectal cancer that are unsuitable for upfront resection (TRICC0808): a multicenter phase II trial comprising the final analysis for survival. Int J Clin Oncol 2019;24:516-25.
16. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005;16:1311-9.
17. Ribero D, Wang H, Donadon M et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007;110:2761-7.
18. Klinger M, Tamandl D, Eipeldauer S et al. Bevacizumab improves pathological response of colorectal cancer liver metastases treated with XELOX/FOLFOX. Ann Surg Oncol 2010;17:2059-65.
19. Tamandl D, Klinger M, Eipeldauer S et al. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. Ann Surg Oncol 2011;18:421-30.
20. Vreuls CP, Van Den Broek MA, Winstanley A et al. Hepatic Sinusoidal Obstruction Syndrome (SOS) reduces

the effect of oxaliplatin in colorectal liver metastases. Histopathology 2012;61:314-8.

21. Umehara M, Umehara Y, Takahashi K et al. Preoperative Chemotherapy with Bevacizumab Extends Disease-free Survival after Resection of Liver Metastases from Colorectal Cancer. Anticancer Res 2016;36:1949-54.
22. Yamazaki K, Nagase M, Tamagawa H et al. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Ann Oncol 2016;27:1539-46.
23. Emmanouilides C, Sfakiotaki G, Androulakis N et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC Cancer 2007;7:91.
24. Gruenberger T, Bridgewater J, Chau I et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomized phase II trial Ann Oncol 2015;26:702-8.
25. Uetake H, Yasuno M, Ishiguro M et al. A multicenter phase II trial of mFOLFOX6 plus bevacizumab to treat liver-only metastases of colorectal cancer that are unsuitable for upfront resection (TRICC0808). Ann Surg Oncol 2015;22:908-15.
26. Demircan NC, Dane F, Ozturk MA et al. Assessment of survival and prognostic factors in metastatic colorectal cancer patients treated with first-line bevacizumab-bases therapy. JBUON 2019;24:1494-1500.
27. Beppu T, Miyamoto Y, Sakamoto Y et al. Chemotherapy and Targeted Therapy for Patients with Initially Unresectable Colorectal Liver Metastases, Focusing on Conversion Hepatectomy and Long-Term Survival. Ann Surg Oncol 2014;21:S405-13.
28. Tomasello G, Petrelli F, Ghidini M, Russo A, Passalacqua R, Barni S. FOLFOXIRI Plus Bevacizumab as Conversion Therapy for Patients With Initially UnresectableMetastatic Colorectal Cancer: A Systematic Review and Pooled Analysis. JAMA Oncol 2017;3:e170278.
29. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38-47.
30. Hatano E, Okuno M, Nakamura K et al. Conversion to complete resection with mFOLFOX6 with bevacizumab or cetuximab based on K-ras status for unresectable colorectal liver metastasis (BECK study). J Hepatobiliary Pancreat Sci 2015;22:634-45.
31. Kucukoner M, Oztekin E, Akdeniz N et al. Prognostic importance of tumor location and anti-EGFR therapy in patients with K-RAS wild type metastatic colorectal cancer. JBUON 2019;24:1501-6.
32. Sakin A, Sahin S, Atci MM. Factors affecting survival in patients with isolated liver-metastatic colorectal cancer treated with local ablative or surgical treatments for liver metastasis. JBUON 2019;24:1801-8.
33. Lieu CH, Renfro LA, de Gramont A et al. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program. J Clin Oncol 2014;32:2975-84.
34. de Haas RJ, Wicherts DA, Salloum C et al. Long term outcomes after hepatic resection for colorectal metastases in young patients. Cancer 2010;116:647-58.