Rationale for Neoadjuvant Chemotherapy of Resectable Colorectal Cancer Liver Metastases: When is it Useful?

Hiroto Kikuchi\textsuperscript{1,2,*}, Shuichi Aoki\textsuperscript{1,3}, Dan G. Duda\textsuperscript{1}, Kohei Shigeta\textsuperscript{1,2}

ABSTRACT

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in the United States (1). Moreover, approximately 20\% of patients are diagnosed with synchronous colorectal liver metastases (CRLMs)(2). For patients with CRLM, the 5-year survival rate with after chemotherapy alone is approximately 11 percent (3). However, the 5-year and 10-year survival rates after surgical resection are reported as 38\% and 26\%, respectively (4). Therefore, surgery is considered a potentially curative intervention in CRLM. Unfortunately, not all CRLM patients are candidate for liver resection due to several factors. These include medical comorbidities and anatomical factors such as the number of metastases, tumor size and margin. In some cases, chemotherapy for unresectable tumors could convert the tumors to resectable. In other cases, neoadjuvant chemotherapy can help patients with synchronous metastatic disease undergo performed staged resection. Although neoadjuvant chemotherapy could be useful, its implementation is not yet standard and its use in resectable CRLM remains controversial. This review article focuses on the potential utility of neoadjuvant therapy for CRLMs.

Key words: colorectal cancer, liver metastases, neoadjuvant chemotherapy, resection, immune checkpoint blockade

RATIONALE FOR LIVER METASTASES RESECTION

Which CRLMs are considered “resectable”? 

Surgical resection is widely regarded as the best intervention to cure and/or achieve long-term survival in CRLM patients. Since liver resection is major surgery, patients must be selected carefully by taking into consideration factors related to patients’ fitness, to the tumors and to their anatomy. Comorbidities, such as other liver diseases, cardiovascular diseases and pulmonary diseases, age and past medical histories can be important risk factors. Factors related to the tumors include established prognostic scoring systems which also evaluate the benefit of neoadjuvant chemotherapy for CRLMs (5-12). The major compo-
ponents in these scoring systems are the size of the largest metastatic lesion, the number of metastases, margin, bilobar liver disease, N and T status, differentiation of primary tumor, CEA level, presence of resectable extrahepatic disease, and interval after primary or liver metastasis. Although few of these scoring systems could predict survival more than 5 years, these scoring are often used for treatment decisions (13). For patients with CRLM who require major liver resection, staged surgery with complementary procedures, such as the portal vein embolization (PVE) (14,15) and the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)(16, 17), could be considered. Finally, regarding the anatomic factors, major limitations for resection could be the number of CRLMs, tumor size, and their location and margins. The continuous progress in the development of neoadjuvant chemotherapy and surgical procedure has simplified the criteria for resectability (18,19).

How about metachronous CRLMs?

Metachronous CRLMs are liver metastases detected after curative surgery of a primary colorectal cancer. The surgical procedure for treating metachronous CRLM is largely similar to the one used for other liver tumors. If an R0 resection is successfully performed for metachronous CRLMs, the 3-year survival and 5-year survival rates after liver resection are reported as 58% and 42%, respectively (4). To estimate the efficacy of neoadjuvant chemotherapy over surgery first, Adam et al analyzed 1,471 patients with solitary and metachronous CRLMs; of these, 169 patients were treated with at least 3 cycles of an oxaliplatin - or irinotecan-based regimen before surgery while 1,302 patients received no preoperative chemotherapy (20). They reported that preoperative chemotherapy did not improve the disease-free survival (DFS) or overall survival (OS) in these patients with CRLMs of less than 5 cm in size. Thus, the benefit of neoadjuvant chemo-therapy remains unclear if the metachronous CRLMs are few, small and easy to resect. However, if the metastatic lesions are multiple or bulky, neoadjuvant chemotherapy may be considered to reduce the burden and the risk of early recurrence after surgery for CRLM, as discussed below.

What is the rationale for using neoadjuvant chemotherapy?

Multiple chemotherapy regimens that include biologics have shown efficacy in metastatic colorectal cancer (mCRC) patients. Some of these regimens have been tested as neoadjuvant chemotherapies for CRLMs, their role and the optimal regimen are still unclear. Because of the potential resistance and/or toxicity to these drugs, the benefit for neoadjuvant chemotherapy for patients with low risk, few and small tumors is questionable. On the other hand, for patients with high risk, unresectable or borderline resectable, neoadjuvant chemotherapy is considered as an appropriate option. Once neoadjuvant chemotherapy is initiated, it is recommended that the CRLM patients are followed by radiographic examination every 6-8 weeks. To evaluate the effect of the regimen, the RECIST criteria are commonly used (21). CRLMs resec- tion should be performed as soon as possible after tumors are deemed resectable, but at least 4 weeks after finishing chemotherapy (or even longer if the antiangiogenic drug bevacizumab is used) to avoid surgical complications.

STANDARD REGIMENS FOR METASTATIC COLORECTAL CANCER

The regimens that have shown efficacy in randomized phase III clinical trials for mCRC are multiple and include doublet or triplet chemotherapies with biologics. Fluorouracil (FU) and leucovorin (LV) are being combined with oxaliplatin or irinotecan or both, regimens referred to as FOLFOX (22), FOLFIRI (23,24) and FOLFOXIRI (25-27), respectively. There are alsomodified options for these regimens (using oral capcitabine (28,29) or S-1 (30,31) instead of FU and LV) that have also shown efficacy in randomized trials. In addition, several molecularly targeted drugs have shown efficacy. These include antiangiogenic (anti-vascular endothelial growth factor (VEGF) pathway) drugs such bevacizumab (anti-VEGF antibody)(32-34), aflibercept (chimeric soluble VEGF receptor (VEGFR)-1 or “VEGF-trap”)(35), ramucirumab (anti-VEGFR2 antibody)(36) and regorafenib (multikinase inhibitor of VEGFRs and RAF)(37), or tumor-targeted drugs such asanti-epithelial growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) (38-40). Cetuximab and panitumumab are only used for patients with wild-type RAS/BRAF status, because these tumors are invariably resistant to EGFR blockade. Moreover, an analysis of six randomized trials of EGFR antibodies showed a better outcome of this intervention for patients with left-sided CRCs than right-sided CRCs (41). This study showed that tumor sidedness could be one of the critical factors for selecting treatment regimens. TAS-102, an oral drug consisting of trifluridine and tipiracil hydrochloride, has also become a treatment
option for mCRC (42). Finally, while immunotherapy with immune checkpoint blockers has failed to show substantial activity so far in mCRC, blockade of programmed cell death receptor (PD)-1 and cytotoxic T lymphocyte associated protein (CTLA)-4 may be an efficacious option for CRC patients with tumors with deficiencies in mismatch repair (dMMR) or high levels of microsatellite instability (MSI-H); this includes the anti-PD-1 antibody nivolumab with or without the anti-CTLA-4 antibody ipilimumab (43). In this study, overall response rate was 55%, and progression-free survival rates were 76% at 9 months and 71% at 1 year. The promising data from the limited experience with immune checkpoint inhibitors in mCRC needs to be validated in larger trials, and its role in other stages of the disease (for example in neoadjuvant setting) remains to be established.

**LIVER TOXICITIES CAUSED BY CHEMOTHERAPY OR BIOLOGICS**

In considering neoadjuvant treatment for CRLM, an important factor is the characteristic liver toxicity of the drugs, which could pose a risk for liver resection (44, 45). Oxaliplatin causes sinusoidal obstruction syndrome, which is similar to a venous occlusive disease. Non-cirrhotic portal hypertension has also been reported for the use of oxaliplatin with fluorouracil (45). Irinotecan can cause steatosis and steatohepatitis – adverse effects which correlate with highmortality (46). A more recent report on liver toxicity after preoperative chemotherapy shows that steatohepatitis was observed more frequently after irinotecan than after oxaliplatin (14.8% vs 3.4%) and in patients with body mass index (BMI) > 25 kg/m² (OR= 10.0)(47). Another paper shows that the preoperative aspartate aminotransferase-to-platelet ratio index can predict liver-related complications after neoadjuvant chemotherapy and is related to sinusoidal obstruction syndrome (48). Bevacizumab is often used with oxaliplatin or irinotecan regimen. However, bevacizumab can cause adverse effects such as thromboembolic disease, bleeding and bowel perforation. In addition, it may also cause delays in wound and liver healing post-surgery (49). Therefore, liver resection is usually planned 6 to 8 weeks after bevacizumab therapy, given its prolonged half-life in blood circulation.

**GUIDELINES FOR INITIALLY RESECTABLE CRLMS**

In the United States of America, the guidelines set by the National Comprehensive Cancer Network (NCCN) recommended upfront surgery if the tumors are initially resectable (50). For cases where there are more than 4 metastases, suspicion of portal node metastasis or bilobar disease, neoadjuvant chemotherapy is preferred prior to surgical resection. Once neoadjuvant chemotherapy starts, it is critically important to check the tumor status every 6 to 8 weeks using radiographic examinations to minimize the number of chemotherapy courses. In some cases, the CRLMs recurr in remaining liver rapidly after resection. Most likely, these CRLMs are present at the time of resection and are particularly aggressive. For these cases, two or three cycles of preoperative chemotherapy may be a useful option to determine whether these CRLM patients will derive benefit from surgical intervention or not (51). In the largest study performed to date, the European Organization for Research and Treatment of Cancer (EORTC) investigators tested whether perioperative chemotherapy can improve survival in CRLM patients over surgery alone (EORTC Intergroup trial 40983). Patients were randomly assigned to receive FOLFOX4 versus surgery upfront (52,53). In this study, 12 weeks of chemotherapy was planned for both pre- and post-operative period. Sixty-seven of 182 patients were included and about 80% of them were resected in both groups. The HR for progression-free survival was 0.79 (p=0.058) in all randomly assigned patients; this corresponded to an increase in median progression-free survival from 11.7 months to 18.7 months with the addition of chemotherapy. This difference was significant in the patients in whom resection was actually achieved after study entry (HR was 0.73, p=0.025). However, after 8.5 years of follow up, there was no significant statistical differences in 5-year overall survival (52,53). Of note, the trial was not powered to detect a difference in overall survival. The study investigators concluded that – while the difference in survival shown in this study was not statistically significant – further evaluation of perioperative chemotherapy with FOLFOX4 (with or without biologics) is warranted for resectable CRLM. In conclusion, the benefit of neoadjuvant chemotherapy remains controversial for initially resectable CRLMs.

**SYSTEMIC NEOADJUVANT THERAPY REGIMENS FOR INITIALLY RESECTABLE CRLMS**

Recently, the number of drugs and regimens that showed efficacy for mCRChas been rapidly increasing. The suggestions included in the NCCN and European
Society for Medical Oncology (ESMO) guidelines for initially resectable CRLMs include the use of FOLFOX, FOLFIRI, XELOX (capecitabine and oxaliplatin) with or without bevacizumab, and FOLFI, FOLFOX with or without cetuximab or panitumumab (54). More recently, FOLFOXIRI was also added in the NCCN guideline as a treatment option for neoadjuvant therapy. Adding bevacizumab to the 5-FU and oxaliplatin regimen may improve pathological responses and reduce liver injury (55). Similarly, adding anti-EGFR antibody to chemotherapies can produce “early tumor shrinkage”, and this effect is associated with superior long-term outcomes (56). While these regimens might be useful, there are some critical points that must be kept in mind for choosing regimens. For the use of anti-VEGF as part of neoadjuvant treatment for patients with resectable CRLMs, the concerns are the potential adverse effects of bevacizumab (49). For the use of anti-EGFR therapy, the concerns is the efficacy of the intervention, as the result of the EPOC trial which showed no difference in OS and an inferior progression-free survival (PFS) when cetuximab was added to FOLFOX (57,58).

Potential systemic therapy regimens for unresectable CRLMs

For patients with initially unresectable CRLMs, there is strong rationale for preoperative chemotherapy. Usually patients with initially un-resectable CRLMs receive at least several courses of chemotherapy to evaluate tumor response and reevaluate the resectability. Longer interventions may cause liver damage, which in turn may cause postoperative complications. If neoadjuvant chemotherapy is effective and converts the unresectable CRLMs to resectable, an immediate liver resection is recommended. There ported success rates for conversion after neoadjuvant therapy range between 12-33% (25,59-66). The reported 5-year survival rate after resection are 30-54%, which is considerably higher than that after chemotherapy alone (approximately 10%). After chemotherapy, the rate of complete pathologic response is reported at 4-9% (60,67,68). Even if CRLMs show complete radiologic response after chemotherapy, the vast majority of cases showed persistent macroscopic or microscopic residual disease or early recurrence in situ (69). Thus, resection is strongly indicated even if the CRLMs show complete response by imaging. In these case, identifying tumor locations is critically important; an option to address this problem is using a marking technique consisting of placing coils using computed tomography or ultrasound guidance before chemotherapy (70).

For initially unresectable CRLMs, all the regimens for unresectable mCRCs are considered appropriate. However, there is no standard regimen for this particular setting. If conversion from initially unresectable or borderline to resectable is expected, there are some recommendations. These include FOLFOX or FOLFOXIRI: for patients with-wild type of RAS and BRAF, FOLFIRI plus cetuximab or panitumumab could also be considered. Since potent cytotoxic regimens are preferred for attempting conversion, doublet therapies which contain either oxaliplatin or irinotecan are usually selected; FOLFOX is more commonly selected than FOLFIRI because irinotecan may cause steatohepatitis. There are some early reports on the use of FOLFOXIRI, which contains both oxaliplatin and irinotecan and appears to be useful for young patients or patients without comorbidities (25,64). From the retrospective analysis of the TRIBE trial, FOLFOXIRI plus bevacizumab may be one of the options for the first-line regimen for patients with right-sided mCRCs regardless of their status of RAS or BRAF mutation, because of their worse prognosis compared to left-sided tumors (71). Finally, while the use of immune checkpoint inhibitors is now standard for unresectable mCRCs with dMMR MSI-H tumors, their safety and utility in neoadjuvant setting remains to be examined.

CONCLUSION

Surgical resection for CRLMs remains the intervention of choice to achieve cure in this advanced disease setting. Although a recent meta-analysis including 18 studies (6,254 patients) shows that neoadjuvant chemo-therapy can improve both 5-year DFS (HR 1.38) and 5-year OS (HR=1.19)(72), there are no currently selection criteria for patients and no prospective evidence to prove the benefit of combining targeted agents such as cetuximab and bevacizumab (73). Therefore, for initially resectable CRLMs, resection is usually recommended if feasible. For initially un-resectable CRLMs, chemotherapy using cytotoxic regimens should be considered to convert the tumors to resectable. With the advent of multiple effective cytotoxic regimens, biologics and immune checkpoint inhibitors for mCRCs, there are great expectations that new systemic neoadjuvant therapy will further improve the survival outcomes. However, the safety and efficacy of these interventions should be tested and validated in future randomized studies.
Conflict of interest

The authors declare no conflict of interest with this work.

REFERENCES

1. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. Cancer. 2018;124(13): 2785-2800.
2. Leporier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg. 2006;93(4):465-74.
3. Ferrarotto R, Pathak P, Manu D, Agarwal A, Overman M, Hoff PM, et al. Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. Clin Colorectal Cancer. 2011; 10(3):178-82.
4. Kanas GP, Taylor A, Primrose JN, Langbein WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283-301.
5. Konopke R, Kersting S, Distler M, Dietrich J, Gastmeier J, Heller A, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int. 2009;29(1):89-102.
6. Nagasawa T, D'Amico G, Naganawa H, Muto T, and O. K. Proposal of a scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer, 1996;77(7):1254-62.
7. Rees M, Tekkis PP, Welsh F, K S, O’Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multivariable model of 929 patients. Ann Surg. 2008; 247(1):125-35.
8. Shizubazu Iwatsuki SD, Madojiga JR, Wallis Marsh J, Dodson F, Bonnham AC, Geller DA, et al. Hepatic Resection for Metastatic Colorectal Adenocarcinoma: A Proposal of a Prognostic Scoring System. J Am Coll Surg. 1999;189(3):291-299.
9. Yokoyama Y, Mori H, Hasegawa M, Tanaka K, Kotera Y, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multivariant data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2012;19(1):72-84.
10. Roberts KJ, White A, Cockbain A, Hodson J, Hidalgo E, Toogood GJ, Lodge JPA. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. Br J Surg. 2014;101(7):856-66.
11. Aoki T, Kubota K. Preoperative portal vein embolization for hepato-cellular carcinoma: Consensus and controversy. World J Hepatol. 2016;8(9):439-45.
12. Makushu M, Takuma T, Yarnazaki S, Hasegawa H, Nishimura S, Shimamura Y. Preoperative transarterial embolization of the portal venous branch for patients receiving extended lobectomy due to the bile duct carcinoma. J Jpn Soc Clin Surg. 1984;45:14-20.
13. de Santibanes E, Clavien PA. Playing Play-Doh to prevent post-operative liver failure: the ‘ALPPS’ approach. Ann Surg. 2012; 255(3):415-7.
14. Schadde E, Schnitzbauer AA, Tschoch C, Rapits DB, Beckweid WD, Clavien PA et al. Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy. Ann Surg Oncol. 2015;22(9):3109-20.
15. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol. 2005;23(33):8490-9.
16. Berri RN, a.E.K.A. Curable Metastatic Colorectal Cancer: Recommended Paradigms. Curr Oncol Rep. 2009;11:200-208.
17. Adam R, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg. 2010;252(3):774-87.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):229-47.
19. Goldberg SM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30.
20. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905-114.
21. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000; 355(9209):1041-1047.
22. Falcone A, Ricci S, Brunetti I, Pfanner E, Giacomo A, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25(13):1670-6.
23. Van Cutsem E, Twelves C, Allman D, Bajetta E, Boyer M, et al. Durable complete responses in metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncology. 2010;11(9):853-860.
24. Cunningham D, Clark M, Bondarenko I, Saura C, Glagov S, Walmsley SR, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer: the AVANCE study. N Engl J Med. 2013;368(23):2191-201.
25. Bonham AC, Geller DA, et al. Hepatic Resection for Metastatic Colorectal Adenocarcinoma: A Proposal of a Prognostic Scoring System. J Am Coll Surg. 1999;189(3):291-299.
26. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. OFLOXOXIRI plus bevacizumab versus OFLIXIRI plus bevacinab in patients with previously untreated metastatic colorectal cancer (AVANCE): an open-label, randomised phase 3 trial. Lancet. 2013;381(9875):1501-1509.
27. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus OFLIRI in patients with previously untreated metastatic colorectal cancer: a randomised phase 3 trial. Lancet. 2013;381(9875):1501-1509.
28. Van Cutsem E, Twelves C, Allman D, Bajetta E, Boyer M, et al. Oral Capecitabine Compared With Intravenous Fluorouracil Plus Leucovorin in Patients With Metastatic Colorectal Cancer: Results of a Large Phase III Study. J Clin Oncol. 2001;19(21): 4057-4106.
29. Cunningham D, Lang I, Marcoullo R, Lorusso V, Ovick J, Bok Shin D, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncology. 2013;14(11):1077-1085.
30. Muro K, Boku N, Shimada Y, Tsui A, Sameshima S, Baba H, et al. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncology. 2010;11(9):853-860.
31. Komatsu Y, Yuiki S, Sogabe S, Fukushima H, Iwana I, Kudo M, et al. Phase II study of combined treatment with irinotecan and S-1 (IRIS) in patients with inoperable or recurrent advanced colorectal cancer (OSCURS Trial). Oncology. 2011;80(1-2): 70-5.
32. Hurwitz H, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, et al. Bevacizumab plus irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. The new england journal of medicine.
33. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013-9.

34. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer; updated results from the BICC-C study. J Clin Oncol. 2008;26(4):689-90.

35. Van Cutsem E, Tabernero J, L. E. M. J. N., Lakem J, Prenen H, Pausová J, Macarulla T, et al. Addition of allibepozor to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499-506.

36. Tabernero J, Yoshino T, Lee Cohn A, Obermannova R, Bodoky G, Garcia-Carbonero R, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16(5):499-508.

37. Grotthey A, Van Cutsem E, Sobiero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-312.

38. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27(5):663-71.

39. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. N Engl J Med. 2009;360(14):1408-1417.

40. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barigel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFIRX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705.

41. Arnold D, Lueza B, Douillard J-Y, Peeters M, Lenz H-J, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with metastatic colorectal cancer treated with chemotherapy and EGFFR direct antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713-1729.

42. Meyer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.

43. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus Ipilimumab in metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.

44. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Prognostic and predictive value of primary tumour side in patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol. 2009;27(11):1829-35.

45. Alberts SR, Horvath WL, Sternfeld WC, Goldemberg RM, Mahoney MR, Dahlil SR, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a post-hoc analysis of the New EPOC randomised controlled trial. Lancet Oncol. 2014;15(6):601-611.

46. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Sirivadana A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet. 2014;383(9920):1271-1277.

47. Pesseux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S, et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol. 2013;31(30):3764-75.

48. Wein A, CR, Kockering T, Martus P, Baum U, Brueck M, Reck T, et al. Impact of surgery on survival in palliative patients with metastatic colorectal cancer after first line treatment with weekly 24-hour infusion of high dose 5-fluorouracil and folinic acid. Annals of Oncology. 2001;12:1721-1727.

49. Adam R, Wicherts DA, de Haas RJ, Cicco O, Lüvi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol. 2009;27(11):1829-35.
65. Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. Cancer Chemother Pharmacol. 2008;62(2):195-201.

66. Beppu T, Miyamoto Y, Sakamoto Y, Imai K, Nitta H, Hayashi H, 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 Suppl 3:S405-13.

67. Adam R, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol. 2008; 26(10): 1635-41.

68. Blazer DG 3rd, Kishi Y, Maru DM, Kopetz S, Shin Chun Y, Overman MJ, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol. 2008;26(33):5344-51.

69. Benoist S, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006;24(24): 3939-45.

70. Zalinski S, Abdalla EK, Mahvash A, Vauthey JN. A marking technique for intraoperative localization of small liver metastases before systemic chemotherapy. Ann Surg Oncol. 2009;16(5): 1208-11.

71. Cremolini C, Antoniotti C, Lonardi S, Bergamo F, Cortesi E, Tomasello G, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. Ann Oncol. 2018;29(7):1528-2534.

72. Liu W, Zhou JG, Sun Y, Zhang L, Xing BC, et al. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. Oncotarget. 2016; 7(24):37277-37287.

73. Ke S, Zhan S, Zhu H, Yan D. Topics related to neoadjuvant chemotherapy for resectable liver metastases from colorectal cancer. J Buon. 2018;23(2):296-301.