**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**Manuscript NO:** 62576

**Manuscript Type:** MINIREVIEWS

**Borderline resectable for colorectal liver metastases: Present status and future perspective**

Kitano Y *et al*. Borderline resectable CRLM

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**Received:** January 12, 2021

**Revised:** April 6, 2021

**Accepted:** July 6, 2021

**Published online:** August 27, 2021

**Abstract**

Surgical resection for colorectal liver metastases (CRLM) may offer the best opportunity to improve prognosis. However, only about 20% of CRLM cases are indicated for resection at the time of diagnosis (initially resectable), and the remaining cases are treated as unresectable (initially unresectable). Thanks to recent remarkable developments in chemotherapy, interventional radiology, and surgical techniques, the resectability of CRLM is expanding. However, some metastases are technically resectable but oncologically questionable for upfront surgery. In pancreatic cancer, such cases are categorized as “borderline resectable”, and their definition and treatment strategies are explicit. However, in CRLM, although various poor prognosis factors have been identified in previous reports, no clear definition or treatment strategy for borderline resectable has yet been established. Since the efficacy of hepatectomy for CRLM was reported in the 1970s, multidisciplinary treatment for unresectable cases has improved resectability and prognosis, and clarifying the definition and treatment strategy of borderline resectable CRLM should yield further improvement in prognosis. This review outlines the present status and the future perspective for borderline resectable CRLM, based on previous studies.

**Key Words:** Borderline resectable; Colorectal liver metastases; Adjuvant chemotherapy; Hepatectomy; Colorectal cancer

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**Citation:** Kitano Y, Hayashi H, Matsumoto T, Kinoshita S, Sato H, Shiraishi Y, Nakao Y, Kaida T, Imai K, Yamashita YI, Baba H. Borderline resectable for colorectal liver metastases: Present status and future perspective . *World J Gastrointest Surg* 2021; 13(8): 756-763

URL: https://www.wjgnet.com/1948-9366/full/v13/i8/756.htm

DOI: https://dx.doi.org/10.4240/wjgs.v13.i8.756

**Core Tip:** At this stage, a clear definition and treatment policy for borderline resectable colorectal liver metastases has not been established. According to previous reports, borderline resectable for colorectal liver metastases is oncologically highly malignant (simultaneous liver metastasis, multiple tumors, large tumor diameter, high level of carcinoembryonic antigen, extrahepatic lesions) or technically difficult (necessity of special procedures such as radiofrequency ablation, portal vein embolization, two-stage hepatectomy, and associating liver partition and portal vein ligation for staged hepatectomy for R0 resection or close to the main vessel), and hepatectomy after preoperative adjuvant chemotherapy is recommended as a treatment policy.

**INTRODUCTION**

Colorectal cancer (CRC) is rising worldwide, with approximately 1.8 million new cases and 800000 deaths annually. The liver is the most frequent organ for metastasis of CRC, and about two-thirds of the causes of death of CRC are attributed to liver metastasis[1]. Liver metastasis is found in about 20% of cases when CRC is diagnosed, and more than half of CRC patients have liver metastasis during the course[2]. Colorectal liver metastases (CRLM) is one of the cancers for which long-term prognosis or curative treatment can be enhanced by the resection of metastatic lesions, and this can provide a 5-year survival rate of about 25%-74%[3]. However, only about 20% of cases are indicated for resection at the time of diagnosis of liver metastasis (categorized as initially resectable). The remaining cases are treated as unresectable cases (initially unresectable), and chemotherapy intended to transition to hepatectomy (conversion therapy) or palliative chemotherapy will be performed[4,5]. Untreated CRLM without extrahepatic lesions has a survival time of less than 1 year. Even in an era of remarkable progress in chemotherapy, the 5-year survival rate of CRLM with chemotherapy alone is extremely low. To achieve long-term survival for CRLM, it is necessary to formulate a treatment strategy aiming at radical hepatic resection for each case. The management of CRLM is difficult because of the absence of data from randomized controlled trials to guide decisions and because of the wide variety of factors involved (*e.g.*, the resectability for CRLM, the management of synchronous CRLM, the timing of surgery, the role of laparoscopic surgery, the type of chemotherapy regimen, pre/postoperative management)[6]. Among these factors, the definition of resectability and the treatment strategies of each disease status to be directed toward potential resectability are indispensable. In pancreatic cancer, initially resectable, borderline resectable, and initially unresectable are clearly defined, and the treatment policy is clearly stated in guidelines from various clinical trials[7-9], but this is not the case for CRLM. In this review, in addition to the initially resectable and initially unresectable categories, we will discuss the definition and treatment strategies for CRLM, focusing on borderline resectable, a category that has not yet been clearly defined.

**Histrical transition in resectability of CRLM**

Hepatectomy for CRLM was first reported in the 1970s, and its effect on prognosis has attracted attention. Wilson and Adson[10] performed hepatectomy in 60 patients with CRLM and revealed that overall survival (OS) was significantly better than in the unresected group (5-year OS; 28% *vs* 0%, *P* < 0.05). Subsequently, prognostic factors were identified in various centers to improve the prognosis after hepatectomy for CRLM. Age, primary lesion staging, simultaneous liver metastasis, tumor diameter, number of liver metastases, bilobar lesions, resection margins, and carcinoembryonic antigen (CEA) levels were among the reported predictors of recurrence after hepatectomy[11-21]. In particular, Fong *et al*[11] analyzed more than 1000 CRLM patients who underwent hepatectomy and found that extrahepatic lesions, positive resected margin of liver metastasis, positive primary lymph node metastasis, simultaneous (< 1 year) liver metastasis, multiple liver metastases, maximum diameter > 5 cm, and CEA > 200 ng/mL were independent poor prognostic factors. Furthermore, the latter five risk factors were shown to have a 5-year survival rate by number (the number of risk factors 0: 60%, 1: 44%, 2: 40%, 3: 20%, 4: 25%, 5: 14%), and the former two (extrahepatic lesions, positive resected margin of liver metastasis) were contraindications for hepatectomy due to early recurrence and poor survival rate after hepatectomy[11]. Because cases with these risk factors were technically resectable, but the prognosis was clearly poor, the issue was how to improve the prognosis in such cases.

The majority of patients with CRLM are initially unresectable, and they must be treated with chemotherapy to achieve resectability because, from previous reports, the prognosis of patients with CRLM is clearly much better if metastases can be removed surgically than if they cannot[4,5]. Before the 1990s, 5-fluorouracil/leucovorin was the only antitumor drug for metastatic CRC. Since 1990, however, oxaliplatin and irinotecan have become available, and doublet therapy (FOLFOX, FOLFIRI) became standard[22]. In the 2000s, with the advent of molecular targeted therapy represented by anti-vascular epidermal growth factor antibody and anti-epidermal growth factor receptor antibody[23], and triplet therapy (FOLFOXIRI) with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan, treatment strategies and results for CRLM have been changing significantly[24,25].

According to a report from Paul Brousse Hospital, a 5-year recurrence-free survival (RFS) rate of 19% could be obtained by the radical resection of metastatic lesions even in cases with extrahepatic diseases, which was comparable to cases without extrahepatic diseases[26]. A 5-year RFS rate of 18% was also obtained for R1 resection in cases without extrahepatic diseases; moreover, it was reported that a 5-year survival rate of 50% or more could be obtained, especially for cases in which chemotherapy was successful[27]. In addition, for cases in which the radical hepatectomy was technically impossible, portal vein embolization (PVE)[28,29], local ablation therapy[30], and two-stage hepatectomy (TSH)[31-34], and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)[35-38] could provide curative resection. As well as the remarkable development of chemotherapy and such special techniques in recent years, it has been important to improve resectability by providing appropriate management, with a multidisciplinary team[39,40]. LiverMetSurvey, an international registration system for CRLM, analyzed more than 25000 cases from 326 institutions in 71 countries, with an initially resectable case with a 5-year survival rate of 46% after hepatectomy. In addition, even in initially unresectable cases, it was reported that a 5-year survival rate of 32% was attainable if hepatectomy could be performed, and long-term survival or cure was expected by multidisciplinary treatment[39,40].

**Present status of resectability for CRLM**

To date, the resectability of CRLM has been divided roughly into two categories, “initially resectable” and “initially unresectable”, and “borderline resectable” has not been discussed in detail. At the 2016 American Society of Clinical Oncology annual meeting, CRLM was divided into three situations (“initially resectable”, “borderline resectable”, “initially unresectable”), but no detailed definition was specified. For initially resectable, surgery without preoperative chemotherapy (hepatectomy that spares parenchyma as much as possible) has been recommended[41,42]. Borderline resectable entailed the possibility of radical resection, but, compared to initially resectable, it was considered to be a situation in which it was difficult to achieve technical or oncological safety. For such patients, hepatectomy after chemotherapy was recommended. For initially unresectable, conversion therapy with triplet therapy as FOLFOXIRI + molecular target drug combination according to KRAS mutation was recommended[42]. In this meeting, the definition of borderline resectable was not addressed.

The 2016 European Society for Medical Oncology guidelines stated that when considering radical hepatectomy for CRLM, resectability must be evaluated from two aspects: The technical category and the oncological category[43]. Furthermore, the technical category was subdivided into “Easy” and “Difficult”, and the Oncological category into “Excellent”, “Good”, and “Bad” from the viewpoint of prognosis. Technical — “Easy”/Oncological — “Excellent” or “Good” cases, in which R0 resection could be achieved by normal hepatectomy that did not require special techniques and the tumor burden was low, were defined as initially resectable. As a treatment strategy, upfront surgery without adjuvant chemotherapy, or surgery with adjuvant chemotherapy for 3 mo before and after surgery, was recommended. Unresectability was defined separately in the technical category and the oncological category, as follows. In the technical category, (A) as absolute non-adaptation; future liver remnant ≥ 30% cannot be guaranteed for R0 resection or the presence of unresectable extrahepatic lesions, (B) as a relative non-adaptation; R0 resection could be achieved only after hepatectomy with special techniques such as PVE, radiofrequency ablation (RFA), TSH, and ALPPS or R1 resection. In the oncological category, (C) simultaneous extrahepatic lesions, five or more liver metastases, and tumor progression during chemotherapy were listed, and if (A) or both (B) and (C) were observed, the metastasis was regarded as initially unresectable. In such cases, conversion therapy or palliative chemotherapy should be administered. Borderline resectable was defined as technically “Easy” but oncologically “Bad”, *i.e.* a case in which R0 surgery was possible without special techniques but had poor prognostic factors in the oncological category. For such cases, due to the high risk of recurrence, hepatectomy was recommended after preoperative chemotherapy with doublet- or triplet-drug chemotherapy.

**Borderline resectable for CRLM**

A search of “colorectal liver metastases” AND “borderline resectable” or “potentially resectable” in the abstract by using the literature search tool PubMed found 76 related reports, but only nine actually referred in detail to borderline resectable as an aspect of CRLM[3,42-49]. The concept of borderline resectable was first discussed by Jean-Nicolas Vauthey in 2007, and the resectable cases of CRLM were a very heterogeneous population; notably, patients with extrahepatic lesions and those with R1 surgery had a clearly poor prognosis. It was therefore argued that they should be treated as a separate population classified as borderline resectable[50]. In 2013, Jones *et al*[44] specified number of tumors ≥ 4, maximum diameter ≥ 5 cm, and CEA ≥ 100 ng/mL as borderline resectable, and because the possibility of recurrence in this cohort was expected to be very high, preoperative chemotherapy before hepatectomy was recommended. Since then, there have been several reports on borderline resectable CRLM. Although there is no consensus on its definition, as reported by American Society of Clinical Oncology and European Society for Medical Oncology, the term applied to oncologically highly malignant cases (simultaneous liver metastasis, multiple occurrences, large tumor diameter, high level of CEA, extrahepatic lesions) or technically difficult cases (necessity of special procedures such as RFA, PVE, TSH, ALPPS for R0 resection or close to the main vessel). For such cases, seven of eight reports argued that neoadjuvant chemotherapy should be given, and one argued that four cycles of neoadjuvant chemotherapy should be given before and after surgery[3,42-48] (Table 1). Three reports debated prognosis, and Ichida *et al*[48] defined borderline resectable as tumor number ≥ 4, maximum diameter ≥ 5 cm, or presence of extrahepatic lesions, and hepatectomy was performed after neoadjuvant chemotherapy. In cases with lower tumor burden, upfront hepatectomy was performed without preoperative treatment, and the prognoses were compared. The RFS rate was significantly worse in the borderline resectable group (5-year RFS rate: 22.1% *vs* 46.5%, hazard ratio = 1.48, *P* = 0.02), but there was no significant difference in OS rate (5-year OS rate: 66.6% *vs* 74.0%, hazard ratio = 1.27, *P* = 0.40)[48]. These findings indicated that preoperative adjuvant chemotherapy might be effective for OS in borderline resectable cases.

**CONCLUSION**

According to previous reports, “borderline resectable” for CRLM is oncologically highly malignant (simultaneous liver metastasis, multiple tumors, large tumor diameter, high level of CEA, extrahepatic lesions) or technically difficult (necessity of special procedures such as RFA, PVE, TSH, and ALPPS for R0 resection or close to the main vessel), and hepatectomy after preoperative adjuvant chemotherapy is recommended as a treatment policy. At this stage, however, a clear definition and a treatment policy for borderline resectable, like those available for pancreatic cancer, have not been established, and therefore analysis using big data or a multicenter randomized controlled trial that examines the use of neoadjuvant chemotherapy for borderline resectable CRLM is needed in the future.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Manfredi S**, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; **244**: 254-259 [PMID: 16858188 DOI: 10.1097/01.sla.0000217629.94941.cf]

3 **Qadan M**, D'Angelica MI. Complex Surgical Strategies to Improve Resectability in Borderline-Resectable Disease. *Curr Colorectal Cancer Rep* 2015; **11**: 369-377 [PMID: 28090195 DOI: 10.1007/s11888-015-0290-5]

4 **Adam R**, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; **240**: 644-657; discussion 657-658 [PMID: 15383792 DOI: 10.1097/01.sla.0000141198.92114.f6]

5 **Adam R**, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009; **27**: 1829-1835 [PMID: 19273699 DOI: 10.1200/JCO.2008.19.9273]

6 **Adam R**, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Teh C, Tejpar S, Van Cutsem E, Vauthey JN, Påhlman L; of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev* 2015; **41**: 729-741 [PMID: 26417845 DOI: 10.1016/j.ctrv.2015.06.006]

7 **Tempero MA**, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, Benson AB 3rd, Binder E, Cardin DB, Cha C, Chiorean EG, Chung V, Czito B, Dillhoff M, Dotan E, Ferrone CR, Hardacre J, Hawkins WG, Herman J, Ko AH, Komanduri S, Koong A, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Scaife C, Thayer S, Weekes CD, Wolff RA, Wolpin BM, Burns J, Darlow S. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 1028-1061 [PMID: 28784865 DOI: 10.6004/jnccn.2017.0131]

8 **Varadhachary GR**, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006; **13**: 1035-1046 [PMID: 16865597 DOI: 10.1245/ASO.2006.08.011]

9 **Versteijne E**, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, Buijsen J, Busch OR, Creemers GM, van Dam RM, Eskens FALM, Festen S, de Groot JWB, Groot Koerkamp B, de Hingh IH, Homs MYV, van Hooft JE, Kerver ED, Luelmo SAC, Neelis KJ, Nuyttens J, Paardekooper GMRM, Patijn GA, van der Sangen MJC, de Vos-Geelen J, Wilmink JW, Zwinderman AH, Punt CJ, van Eijck CH, van Tienhoven G; Dutch Pancreatic Cancer Group. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020; **38**: 1763-1773 [PMID: 32105518 DOI: 10.1200/JCO.19.02274]

10 **Wilson SM**, Adson MA. Surgical treatment of hepatic metastases from colorectal cancers. *Arch Surg* 1976; **111**: 330-334 [PMID: 1259571 DOI: 10.1001/archsurg.1976.01360220026004]

11 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-318; discussion 318-321 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

12 **Nordlinger B**, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer* 1996; **77**: 1254-1262 [PMID: 8608500]

13 **Zakaria S**, Donohue JH, Que FG, Farnell MB, Schleck CD, Ilstrup DM, Nagorney DM. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg* 2007; **246**: 183-191 [PMID: 17667495 DOI: 10.1097/SLA.0b013e3180603039]

14 **Foster JH**. Survival after liver resection for secondary tumors. *Am J Surg* 1978; **135**: 389-394 [PMID: 626320 DOI: 10.1016/0002-9610(78)90072-7]

15 **Adson MA**, van Heerden JA, Adson MH, Wagner JS, Ilstrup DM. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; **119**: 647-651 [PMID: 6732473 DOI: 10.1001/archsurg.1984.01390180015003]

16 **Fortner JG**, Silva JS, Golbey RB, Cox EB, Maclean BJ. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. *Ann Surg* 1984; **199**: 306-316 [PMID: 6703792 DOI: 10.1097/00000658-198403000-00010]

17 **Butler J**, Attiyeh FF, Daly JM. Hepatic resection for metastases of the colon and rectum. *Surg Gynecol Obstet* 1986; **162**: 109-113 [PMID: 3945888]

18 **Cobourn CS**, Makowka L, Langer B, Taylor BR, Falk RE. Examination of patient selection and outcome for hepatic resection for metastatic disease. *Surg Gynecol Obstet* 1987; **165**: 239-246 [PMID: 3629438]

19 **Scheele J**, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59-71 [PMID: 7740812 DOI: 10.1007/BF00316981]

20 **Nordlinger B**, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. *Ann Surg* 1987; **205**: 256-263 [PMID: 3827361 DOI: 10.1097/00000658-198703000-00007]

21 **Schlag P**, Hohenberger P, Herfarth C. Resection of liver metastases in colorectal cancer--competitive analysis of treatment results in synchronous *vs* metachronous metastases. *Eur J Surg Oncol* 1990; **16**: 360-365 [PMID: 2379594]

22 **Alberts SR**, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, Levitt R, Rowland K, Nair S, Sargent DJ, Donohue JH. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005; **23**: 9243-9249 [PMID: 16230673 DOI: 10.1200/JCO.2005.07.740]

23 **Stintzing S**, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Giessen-Jung C, Moehler M, Jagenburg A, Kirchner T, Jung A, Heinemann V; FIRE-3 investigators. FOLFIRI plus cetuximab *vs* FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol* 2016; **17**: 1426-1434 [PMID: 27575024 DOI: 10.1016/S1470-2045(16)30269-8]

24 **Adam R**, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Teh C, Van Cutsem E; Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; **17**: 1225-1239 [PMID: 22962059 DOI: 10.1634/theoncologist.2012-0121]

25 **Cremolini C**, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, Mezi S, Tomasello G, Ronzoni M, Zaniboni A, Tonini G, Carlomagno C, Allegrini G, Chiara S, D'Amico M, Granetto C, Cazzaniga M, Boni L, Fontanini G, Falcone A. FOLFOXIRI plus bevacizumab *vs* FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015; **16**: 1306-1315 [PMID: 26338525 DOI: 10.1016/S1470-2045(15)00122-9]

26 **Imai K**, Castro Benitez C, Allard MA, Vibert E, Sa Cunha A, Cherqui D, Castaing D, Bismuth H, Baba H, Adam R. Potential of a cure in patients with colorectal liver metastases and concomitant extrahepatic disease. *J Surg Oncol* 2017; **115**: 488-496 [PMID: 28369939 DOI: 10.1002/jso.24539]

27 **Hosokawa I**, Allard MA, Gelli M, Ciacio O, Vibert E, Cherqui D, Sa Cunha A, Castaing D, Miyazaki M, Adam R. Long-Term Survival Benefit and Potential for Cure after R1 Resection for Colorectal Liver Metastases. *Ann Surg Oncol* 2016; **23**: 1897-1905 [PMID: 26822881 DOI: 10.1245/s10434-015-5060-8]

28 **Wicherts DA**, de Haas RJ, Andreani P, Sotirov D, Salloum C, Castaing D, Adam R, Azoulay D. Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. *Br J Surg* 2010; **97**: 240-250 [PMID: 20087967 DOI: 10.1002/bjs.6756]

29 **Makuuchi M**, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, Yamazaki S, Hasegawa H, Ozaki H. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990; **107**: 521-527 [PMID: 2333592]

30 **Imai K**, Allard MA, Castro Benitez C, Vibert E, Sa Cunha A, Cherqui D, Castaing D, Baba H, Adam R. Long-term outcomes of radiofrequency ablation combined with hepatectomy compared with hepatectomy alone for colorectal liver metastases. *Br J Surg* 2017; **104**: 570-579 [PMID: 28112813 DOI: 10.1002/bjs.10447]

31 **Imai K**, Benitez CC, Allard MA, Vibert E, Cunha AS, Cherqui D, Castaing D, Bismuth H, Baba H, Adam R. Failure to Achieve a 2-Stage Hepatectomy for Colorectal Liver Metastases: How to Prevent It? *Ann Surg* 2015; **262**: 772-778; discussion 778-779 [PMID: 26583665 DOI: 10.1097/SLA.0000000000001449]

32 **Adam R**, Miller R, Pitombo M, Wicherts DA, de Haas RJ, Bitsakou G, Aloia T. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. *Surg Oncol Clin N Am* 2007; **16**: 525-536, viii [PMID: 17606192 DOI: 10.1016/j.soc.2007.04.016]

33 **Adam R**, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; **232**: 777-785 [PMID: 11088072 DOI: 10.1097/00000658-200012000-00006]

34 **Wicherts DA**, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan LA, Azoulay D, Bismuth H, Castaing D, Adam R. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann Surg* 2008; **248**: 994-1005 [PMID: 19092344 DOI: 10.1097/SLA.0b013e3181907fd9]

35 **Schnitzbauer AA**, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012; **255**: 405-414 [PMID: 22330038 DOI: 10.1097/SLA.0b013e31824856f5]

36 **de Santibañes E**, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. *Ann Surg* 2012; **255**: 415-417 [PMID: 22330039 DOI: 10.1097/SLA.0b013e318248577d]

37 **Sandström P**, Røsok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, Schultz NA, Bjørnbeth BA, Isaksson B, Rizell M, Björnsson B. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). *Ann Surg* 2018; **267**: 833-840 [PMID: 28902669 DOI: 10.1097/SLA.0000000000002511]

38 **Hasselgren K**, Røsok BI, Larsen PN, Sparrelid E, Lindell G, Schultz NA, Bjørnbeth BA, Isaksson B, Larsson AL, Rizell M, Björnsson B, Sandström P. ALPPS Improves Survival Compared With TSH in Patients Affected of CRLM: Survival Analysis From the Randomized Controlled Trial LIGRO. *Ann Surg* 2021; **273**: 442-448 [PMID: 32049675 DOI: 10.1097/SLA.0000000000003701]

39 **Adam R**, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. *Ann Gastroenterol Surg* 2019; **3**: 50-56 [PMID: 30697610 DOI: 10.1002/ags3.12227]

40 **Jones RP**, Vauthey JN, Adam R, Rees M, Berry D, Jackson R, Grimes N, Fenwick SW, Poston GJ, Malik HZ. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. *Br J Surg* 2012; **99**: 1263-1269 [PMID: 22864887 DOI: 10.1002/bjs.8835]

41 **Gold JS**, Are C, Kornprat P, Jarnagin WR, Gönen M, Fong Y, DeMatteo RP, Blumgart LH, D'Angelica M. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg* 2008; **247**: 109-117 [PMID: 18156930 DOI: 10.1097/SLA.0b013e3181557e47]

42 **Kaczirek K**. ASCO 2016 - update colorectal liver metastases. *Memo* 2017; **10**: 103-105 [PMID: 28725278 DOI: 10.1007/s12254-016-0308-y]

43 **Van Cutsem E**, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386-1422 [PMID: 27380959 DOI: 10.1093/annonc/mdw235]

44 **Jones RP**, Malik HZ, Fenwick SW, Poston GJ. Perioperative chemotherapy for resectable colorectal liver metastases: where now? *Eur J Surg Oncol* 2013; **39**: 807-811 [PMID: 23726258 DOI: 10.1016/j.ejso.2013.04.002]

45 **Worni M**, Shah KN, Clary BM. Colorectal cancer with potentially resectable hepatic metastases: optimizing treatment. *Curr Oncol Rep* 2014; **16**: 407 [PMID: 25129331 DOI: 10.1007/s11912-014-0407-z]

46 **Pietrantonio F**, Di Bartolomeo M, Cotsoglou C, Mennitto A, Berenato R, Morano F, Coppa J, Perrone F, Iacovelli R, Milione M, Alessi A, Vaiani M, Bossi I, Ricchini F, Scotti M, Caporale M, Bajetta E, de Braud F, Mazzaferro V. Perioperative Triplet Chemotherapy and Cetuximab in Patients With RAS Wild Type High Recurrence Risk or Borderline Resectable Colorectal Cancer Liver Metastases. *Clin Colorectal Cancer* 2017; **16**: e191-e198 [PMID: 27979717 DOI: 10.1016/j.clcc.2016.09.007]

47 **Bonadio RC**, Amor Divino PH, Obando JSM, Lima KCA, Recchimuzzi DZ, Kruger JAP, Saragiotto DF, Capareli FC, Hoff PM. Conversion Chemotherapy With a Modified FLOX Regimen for Borderline or Unresectable Liver Metastases From Colorectal Cancer: An Alternative for Limited-Resources Settings. *J Glob Oncol* 2019; **5**: 1-6 [PMID: 31479339 DOI: 10.1200/JGO.19.00180]

48 **Ichida H**, Mise Y, Ito H, Ishizawa T, Inoue Y, Takahashi Y, Shinozaki E, Yamaguchi K, Saiura A. Optimal indication criteria for neoadjuvant chemotherapy in patients with resectable colorectal liver metastases. *World J Surg Oncol* 2019; **17**: 100 [PMID: 31196104 DOI: 10.1186/s12957-019-1641-5]

49 **Phelip JM**, Mineur L, De la Fouchardière C, Chatelut E, Quesada JL, Roblin X, Pezet D, Mendoza C, Buc E, Rivoire M. High Resectability Rate of Initially Unresectable Colorectal Liver Metastases After UGT1A1-Adapted High-Dose Irinotecan Combined with LV5FU2 and Cetuximab: A Multicenter Phase II Study (ERBIFORT). *Ann Surg Oncol* 2016; **23**: 2161-2166 [PMID: 26739304 DOI: 10.1245/s10434-015-5072-4]

50 **Vauthey JN**. Colorectal liver metastases: treat effectively up front and consider the borderline resectable. *J Clin Oncol* 2007; **25**: 4524-4525 [PMID: 17925547 DOI: 10.1200/JCO.2007.13.1136]

**Footnotes**

**Conflict-of-interest statement:** No conflict of interest exists in this study.

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**Manuscript source:** Invited manuscript

**Peer-review started:** January 12, 2021

**First decision:** March 30, 2021

**Article in press:** July 6, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Japan

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Fu T **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:** Yuan YY

**Table 1 Definition and treatment strategy for borderline resectable colorectal liver metastases in previous studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Definition** | **Treatment** | **Prognosis** |
| Jones *et al*[44], 2013 | Synchronous (< 12 mo); Bilobar diseases: Number ≥ 4; Size ≥ 5 cm; CEA ≥ 100 ng/mL | NAC (FOLFOX) | - |
| Worni *et al*[45], 2014 | Bilobar diseases; Proximity to vascular or biliary structure; Low FLR | NAC | - |
| Qadan *et al*[3], 2015 | Low FLR (< 20%, < 2 contiguous segments); Extrahepatic diseases; R1: Number ≥ 4 | NAC (doublet or triplet) | - |
| Kaczirek *et al*[42], 2017 | - | NAC (doublet + bevacizumab) | - |
| Phelip *et al*[49], 2016 | 3 ≤ Number < 8; ≤ 6 segments involvement; Without infiltration of HA, HV, and PV; Extrahepatic diseases ≤ 2 | NAC (FOLFIRI) | 3-yr PFS: 23.3%; 3-yr OS: 66.1% |
| Van Cutsem *et al*[43], 2016 | Extrahepatic diseases: Number ≥ 5; Tumor progression | NAC (doublet or triplet) | - |
| Pietrantonio *et al*[46], 2017 | > 1 hepatic vein involvement; > 4 segments involvement; Necessity of RFA or TSH; Number ≥ 4; Synchronous | Pre/post 4 cycle chemotherapy (COI-E) | Median PFS 17.8 mo; Median OS 62.5 mo |
| Bonadio *et al*[47], 2019 | Number ≥ 4; Proximity to vascular or biliary structure | NAC (mFLOX) | Median PFS 16.9 mo; Median OS 68.3 mo |
| Ichida *et al*[48], 2019 | Number ≥ 4; Size ≥ 5 cm; Extrahepatic diseases | NAC (doublet) | BR-NAC *vs* resectable: 5-yr RFS: 22.1% *vs* 46.5%, *P* = 0.02; 5-yr OS: 66.6% *vs* 74.0%, *P* = 0.40 |

CEA: Carcinoembryonic antigen; FLR: Future liver remnant; HA: Hepatic artery; HV: Hepatic vein; PV: Portal vein; RFA: Radiofrequency ablation; TSH: Two-stage hepatectomy; NAC: Neoadjuvant chemotherapy; FOLFOX: Infusional 5-fluorouracil, leucovorin, and oxaliplatin; COI-E: Cetuximab, irinotecan, oxaliplatin, and capecitabine; mFLOX, modified fluorouracil, leucovorin, and oxaliplatin; PFS: Progression-free survival; OS: Overall survival; BR: Borderline resectable; RFS: Recurrence-free survival.



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