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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Damiano Caputo, FACS, MD, Associate Professor, Surgeon, Department of General Surgery, Università Campus Bio-Medico di Roma, Rome 00128, Italy. d.caputo@unicampus.it

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

Yuki Kitano, Hiromitsu Hayashi, Takashi Matsumoto, Shotaro Kinoshita, Hiroki Sato, Yuta Shiraishi, Yosuke Nakao, Takayoshi Kaida, Katsunori Imai, Yo-ichi Yamashita, Hideo Baba

ORCID number: Yuki Kitano 0000-0001-6292-8670; Hiromitsu Hayashi 0000-0002-1832-4287; Takashi Matsumoto 0000-0001-6791-6441; Shotaro Kinoshita 0000-0002-6690-4702; Hiroki Sato 0000-0001-5213-018X; Yuta Shiraishi 0000-0002-8064-2163; Yosuke Nakao 0000-0002-6156-1421; Takayoshi Kaida 0000-0002-9134-6124; Katsunori Imai 0000-0003-0549-1825; Yo-ichi Yamashita 0000-0001-8439-6660; Hideo Baba 0000-0002-3474-2550.

Author contributions: Kitano Y, Hayashi H, Imai K, Yamashita YI and Baba H contributed conception and design; Kitano Y, Hayashi H, Matsumoto T, Kinoshita S, Sato H, Shiraishi Y, Nakao Y, Kaida T, Imai K, Yamashita YI, and Baba H contributed writing, review, and/or revision of the manuscript; Kitano Y, Hayashi H, Imai K, Yamashita YI, and Baba H contributed study supervision.

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Yuki Kitano, Hiromitsu Hayashi, Takashi Matsumoto, Shotaro Kinoshita, Hiroki Sato, Yuta Shiraishi, Yosuke Nakao, Takayoshi Kaida, Katsunori Imai, Yo-ichi Yamashita, Hideo Baba, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-8556, Japan

Corresponding author: Hiromitsu Hayashi, FACS, MD, PhD, Assistant Professor, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Kumamoto 860-8556, Japan. hhayasi@kumamoto-u.ac.jp

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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Core Tip: At this stage, a clear definition and treatment policy for borderline resectable

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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.

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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.

HISTORICAL 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 $\geq 30\%$ 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.

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

Ref.	Definition	Treatment	Prognosis
Jones <i>et al</i> [44], 2013	Synchronous (< 12 mo); Bilobar diseases; Number ≥ 4; Size ≥ 5 cm; CEA ≥ 100 ng/mL	NAC (FOLFOX)	-
Worni <i>et al</i> [45], 2014	Bilobar diseases; Proximity to vascular or biliary structure; Low FLR	NAC	-
Qadan <i>et al</i> [3], 2015	Low FLR (< 20%, < 2 contiguous segments); Extrahepatic diseases; R1: Number ≥ 4	NAC (doublet or triplet)	-
Kaczirek <i>et al</i> [42], 2017	-	NAC (doublet + bevacizumab)	-
Phelip <i>et al</i> [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 <i>et al</i> [43], 2016	Extrahepatic diseases: Number ≥ 5; Tumor progression	NAC (doublet or triplet)	-
Pietrantonio <i>et al</i> [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 <i>et al</i> [47], 2019	Number ≥ 4; Proximity to vascular or biliary structure	NAC (mFLOX)	Median PFS 16.9 mo; Median OS 68.3 mo
Ichida <i>et al</i> [48], 2019	Number ≥ 4; Size ≥ 5 cm; Extrahepatic diseases	NAC (doublet)	BR-NAC <i>vs</i> resectable: 5-yr RFS: 22.1% <i>vs</i> 46.5%, <i>P</i> = 0.02; 5-yr OS: 66.6% <i>vs</i> 74.0%, <i>P</i> = 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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