Review Article

Japanese experience with hepatic resection of *KRAS*-mutated colorectal liver metastases

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Abstract: *RAS* mutation is a well-known prognostic marker predicting patterns of recurrence and survival after resection of colorectal liver metastases (CLMs). However, there has been scarce evidence regarding the optimal choice of treatment for *RAS*-mutated CLMs. Indeed, *RAS*-mutated CLMs are at high risk of lung metastases which may preclude curative-intent treatment at the time of recurrence. Nevertheless, aggressive surgical approach using repeated resection for recurrent lesions may have prognostic advantage regardless of the *RAS* mutational status. As such, basic management of CLMs including careful work-up, preoperative chemotherapy for oncologically unfavorable cases, curative-intent surgery, adjuvant chemotherapy for synchronous disease, and careful follow-up including thoracic scan for monitoring the lung metastases would be important to maximize the survival outcomes of patients with CLMs irrespective of *RAS* mutational status.

Keywords: Colorectal liver metastases (CLMs); resection; chemotherapy; KRAS

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Introduction

Multidisciplinary treatment approach including liver resection and chemotherapy has been reported as an effective strategy to improve the long-term outcomes of patients with colorectal liver metastases (CLM) (1). Because clinical courses of individual patients are highly influenced by their oncological and physical statuses (2-4), risk stratification before selecting a treatment is important to maximize the treatment outcomes especially for the patients with advanced disease.

In the era of precision medicine, emerging biologic markers such as *RAS*, *BRAF*, *PIK3CA*, *TP53*, or *SMAD4* have been reported to be associated with oncological aggressiveness of tumors and treatment outcomes of patients with CLM (5-19). *RAS* mutation is a well-known prognostic marker predicting patterns of recurrence and survival (12,14,20-22) after resection of CLM. Given that mutation in *RAS* is reported to be associated with a risk of histologically narrower surgical margin (23,24) and a higher risk of lung metastases (12,14,22), intensive multidisciplinary treatment approach is usually required for the patients with *RAS*-mutated CLM.

In this review, optimal treatment approach for CLM is revisited and clinical features of *RAS*-mutated CLM is discussed based on our experience at a Japanese high-volume center.

Significance of surgical resection for CLMs

While CLM is a stage IV cancer by definition, optimal therapeutic intervention may prolong survival outcomes, and we can even expect "cure" in selected population through a multidisciplinary treatment approach. Several observational studies have reported that surgical resection is an effective treatment for improving long-term survival of patients with CLM (1,25), and the current clinical guidelines have included "conversion to surgery" as a part

Table 1 The preoperative score predicting disease-free survival after hepatic resection for colorectal liver metastases [adopted from Beppu *et al*. (28) with permission]

Risk factors	Preoperative score
Timing of liver metastases	
Metachronous	0
Synchronous	3
Primary tumor LN status	
Negative	0
Positive	3
Number of tumors	
1	0
2–4	4
≥5	9
Largest tumor diameter	
≤5 cm	0
>5 cm	2
Extrahepatic metastatic disease (at hepatectomy)	
No	0
Yes	4
CA19-9 level (before hepatectomy)	
≤100 U/mL	0
>100 U/mL	4

LN, lymph node.

of treatment algorithms for stage IV colorectal cancer (26). From a hepatobiliary surgeon's standpoint, however, the current clinical guidelines do not appropriately present surgical indication for CLM because cytoreduction (i.e., shrinkage of tumor) is not always a requisite condition for curative surgery.

The requisite condition for cure of CLMs: indication criteria for surgery

Theoretically thinking, if we can achieve complete removal of cancerous tissue, the patients will enjoy long-term survival. However, considering that surgery is a local therapy, the patients who will be benefitted from surgery should have localized disease. To meet the theoretical requisite for cure, surgical indication of CLM should be determined considering both "oncological" and "technical" standpoints (27).

Oncological resectability is dependent on the disease control probability with surgery. In many centers, clinical factors such as tumor size, number of nodules, timing of metastases (i.e., synchronous *vs*. metachronous), or presence of extrahepatic disease have been used as prognostic factors to predict the efficacy of surgery. A risk score established based on a Japanese nation-wide survey (28) has clarified prognostic weight of each clinical variable (*Table 1*). Considering that tumor number and synchronous presentation are two potent prognostic factors predicting worse survival outcomes, we usually perform a short course (4–6 cycles in general) preoperative chemotherapy for patients who have such unfavorable factors to confirm the oncological aggressiveness of the disease and curative potential with surgery.

Technical resectability criteria include (I) expectation of margin-negative resection and (II) sufficient volume of future liver remnant. For risk estimation of postoperative hepatic insufficiency, we have used original criteria, expanding conventional Makuuchi's criteria (29). In short, (I) serum bilirubin level <2.0 mg/dL, II) no or controllable ascites, and (III) estimated indocyanine green disappearing rate of the future liver remnant (ICG-Krem) ≥0.05 which is calculated with ICG clearance test and three-dimensional volumetry of the liver (30). When a patient does not meet the volume criteria, portal vein embolization or two stage hepatectomy is considered.

Preoperative chemotherapy and goal of the treatment

Before starting discussion about the significance of preoperative chemotherapy, we should revisit the goal of chemotherapy for the patients with resectable or potentially resectable CLMs. As I mentioned above, tumor shrinkage is not always a goal of chemotherapy. *Figure 1* illustrates the concept and purpose of preoperative chemotherapy. There is a wide range of patient group with marginally resectable disease between the definitely resectable and unresectable diseases. Given that marginally resectable diseases are technically resectable in most of the cases, while they have oncologically unfavorable factors for surgery, the purposes of chemotherapy should be different from "conversion" in such situation.

Conversion is the term used when unresectable disease is "converted" to potentially resectable disease usually through

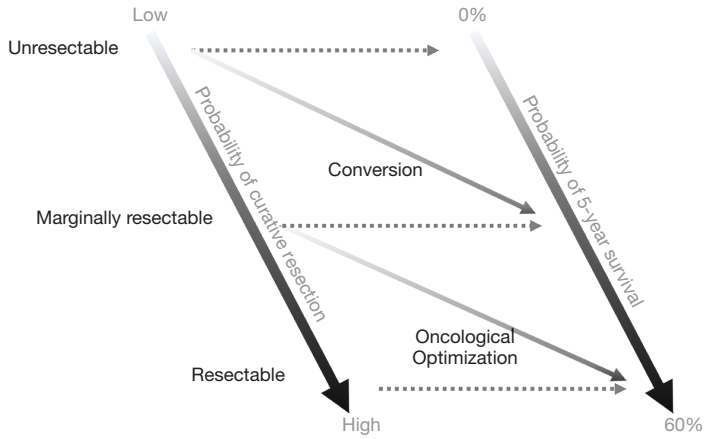


Figure 1 Concept and purpose of preoperative chemotherapy for colorectal liver metastases.

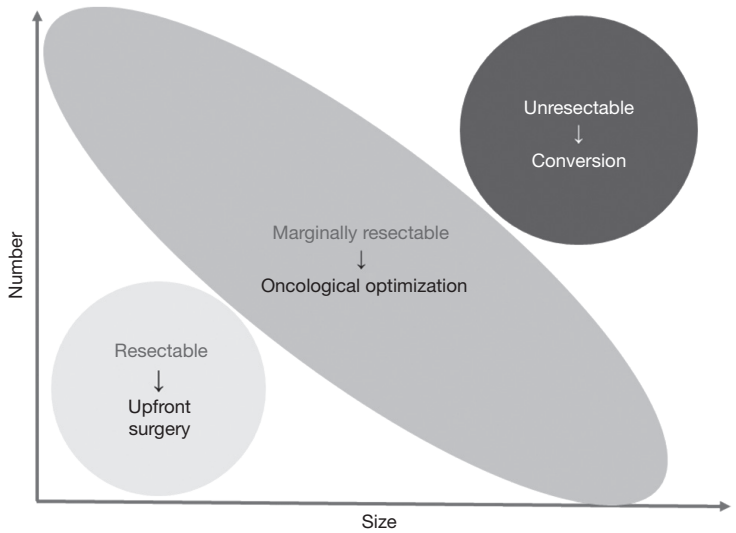


Figure 2 Resectability of colorectal liver metastases according to size and number of tumors.

a good response to chemotherapy. On the other hand, when a patient has CLMs which are technically resectable but oncologically unfavorable for surgery, we should wait and watch under a short course of chemotherapy to confirm the potential benefit of surgery. This group of patients actually have technically resectable disease and the term of "conversion" is not appropriate. Given that we select patients in whom surgical resections are oncologically meaningful in this process, we call this type of chemotherapy "oncological optimization (for surgery)".

Although maximum tumor shrinkage would be the primary goal for conversion to surgery among the initially unresectable diseases, the goal of treatment is relatively complex when treating patients with marginally resectable disease. *Figure 2* illustrate the concept of "resectable", "marginally resectable", and "unresectable" diseases according to the size and numbers of tumors. Because marginally resectable tumors include quite heterogeneous population from solitary, huge tumor to multiple, tiny nodules, the main goal of the preoperative therapy should be different according to the oncological characteristics of individual tumors. Empirically, among patients with marginally resectable CLMs, shrinkage of tumor rarely changes planned surgical procedures, though the surgical maneuver may become less technically demanding. Medical oncologists tend to think that surgical procedure would be

less invasive based on the dogma that degree of resection can be smaller as the tumors shrink with chemotherapy. Several studies have shown that volume of the normal liver parenchyma does not increase and sometimes shrinks with evidence of decreased hepatic functional reserve (31-33). Considering that prolonged chemotherapy does not improve pathologic response rate (34) and may induce chemotherapy-associated liver injury (35-37) length of preoperative chemotherapy should be short as possible when durable response is observed. Furthermore, it has been reported that regardless of the presence of size-based response, long-term outcomes are better when pathological (38) and/or radiological morphologic response (39-41) is observed. Suboptimal pathological response and morphologic response are reportedly associated with presence and wide distribution of microsatellite lesions surrounding macroscopic CLMs (42), and these observations support that narrow margin status may not affect long-term outcomes when pathological or morphologic response is observed after chemotherapy (43).

Basic surgical maneuver for CLMs

Different from hepatocellular carcinoma that requires anatomic resection of the tumor-bearing portal territories (44), CLM can be cured basically with parenchymal sparing surgery. To expect long-term survival of patients with CLM, repeated resection of resectable recurrence is important and the clinical impact of repeated treatment for recurrence after resection has been reported as a concept of time-to-surgical failure (45). In this context, salvageability for recurrent lesions is important, and it has been shown that parenchymal sparing surgery is better than major hepatectomy in terms of higher salvageability and prolonged survival outcomes (46).

Basic principle of adjuvant therapies in the context of time-to-surgical failure

In patients with CLMs, recurrence after surgery does not mean failure of treatment. Empirically, most of the liver lesions are emerging within 2 years after the removal of primary lesion without chemotherapy during the clinical course. Although there has been scarce evidence regarding the necessity of adjuvant therapies after resection of CLM (47,48), a randomized controlled trial has shown that oral adjuvant therapy reduces recurrence-free survival (RFS) rates (49), and our group also confirmed that adjuvant therapy may decrease recurrence and improve survival outcomes regardless of the chemotherapy regimens (50). Considering that prolonged chemotherapy with modern regimens such as FOLFOX or FOLFIRI may induce liver injury that can be an obstacle for repeated resection, we have adopted oral Uracil-Tegafur with Leucovorin (6 months in total) as a 1st choice for adjuvant therapy after resection of CLM.

Surgical outcomes of *RAS*-mutated CLM

A review of 163 patients with a known *KRAS* exon-2 mutation status who underwent curative resection for CLM at 2 Japanese high-volume centers revealed that *KRAS* exon-2 mutation was associated with poorer RFS, shorter time to surgical failure (TSF) (45), and poorer disease-specific survival (DSS) rates (12). *KRAS* exon-2 mutation showed significant association especially with lung metastases, and it was the main cause of early TSF, regardless of the sideness of primary lesions.

When reviewing 139 patients who underwent curative liver resections for CLM with a known RAS status during the last decade at Toranomon Hospital, *RAS*-mutated group showed significantly shorter TSF (34.5 *vs*. 14.0 months; P<0.001) and shorter overall survival (5-year survival rates, 60.7% *vs*. 39.8%, P=0.001) (*Figure 3*) in line with the previous report (12). Proportion of *RAS*-mutated cases decreased as the number of hepatectomy increases (initial hepatectomy, 42.5%; 2nd hepatectomy, 27.7%; 3rd hepatectomy, 20.0%; and 4th hepatectomy, 0%: P=0.006), reflecting that unresectable recurrence is more frequent among the patients with *RAS*-mutated CLMs.

Response to chemotherapy of *RAS*-mutated CLM

RAS status is nowadays used in our daily practice for predicting potential response to anti-EGFR antibodies. However, its utility in prediction of response to the other regimens remains unclear. In a group of patients with heavily treated with bevacizumab, careful pathological and radiological reviews have shown that *RAS* mutation was potentially associated with poor pathologic and radiological morphologic responses (15). Although similar tendency was also observed in a Japanese population, its reproducibility has never been proven in external cohorts.

Our group previously performed comprehensive sequencing of 578 cancer-related genes and showed that MICA gene could be a potential biomarker in prediction

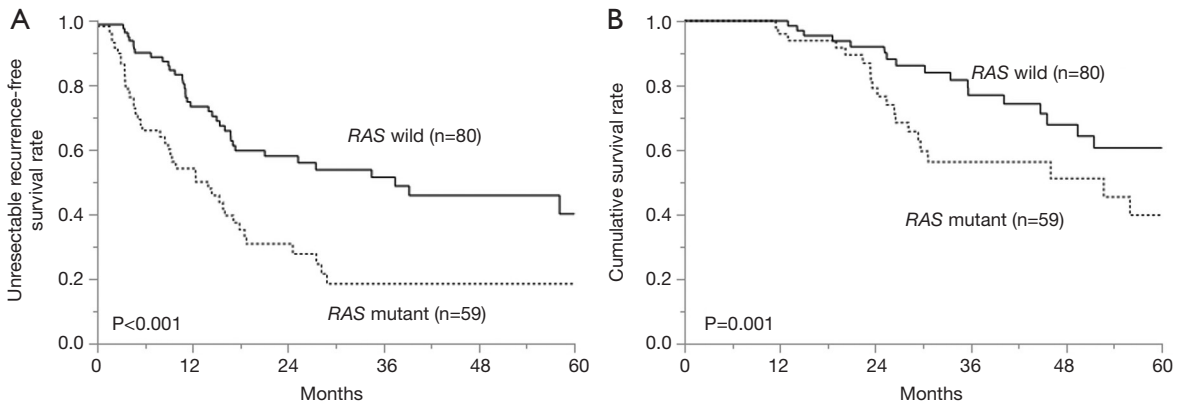


Figure 3 Survival outcomes according to *RAS* mutational status: latest series at Toranomon Hospital. (A) Time-to-surgical failure; (B) overall survival.

of response to chemotherapy with bevacizumab and survival outcomes (51). The *MICA* gene is a member of the major histocompatibility complex (MHC) class I chain-related genes family, encoding a membrane-bound protein that function as a ligand to stimulate NKG2D expressed on all human natural killer and γδ T cells. There are 5 known variants in the *MICA* gene, and the study showed that *MICA* A5.1 variant was associated with better pathologic response (38)/morphologic response (39,41) to bevacizumab, regardless of the *RAS* mutational status. Also, *MICA* A5.1 was associated with a decreased risk of recurrence after resection of CLM. Since somatic mutation is quite rare in the *MICA* gene and very high concordance rate in the *MICA* variant (96.6%) was confirmed between CLM tissue and normal liver parenchyma, these results suggested that the genetic background of the host could be a potential biomarker for CLM. Because bevacizumab has a potential to suppress angiogenesis and modulate immune environments in cancerous tissue, such genetic difference among the host influencing immune response might be associated with the efficacy of bevacizumab. Because response to chemotherapy is not determined only by the *RAS* mutational status of CLM, further studies would be needed including the analysis of genetic background of the host to optimize the treatment approach for the patients with *RAS*-mutated CLMs.

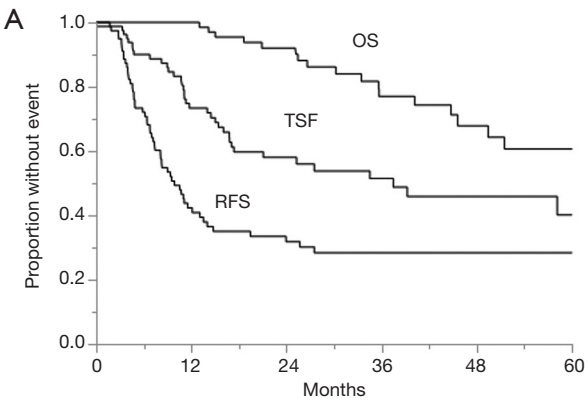
Treatment strategy for *RAS*-mutated CLM: lessons from long-term survivors

Of the 59 patients with *RAS*-mutated CLM treated at our institution, there were 11 patients who survived without unresectable recurrence more than 1 year from the initial hepatectomy. Although no specific clinical factors including size, number of tumors, primary sideness, primary nodal status, location of *RAS* mutation, disease free interval from resection of primary lesion, or perioperative chemotherapy was identified as a potential predictor for survival, 4 out of the 11 patients developed recurrence during the observational period (liver, n=4; lung, n=1; hilar lymph node, n=1; right adrenal gland, n=1) and all of them were curatively resected.

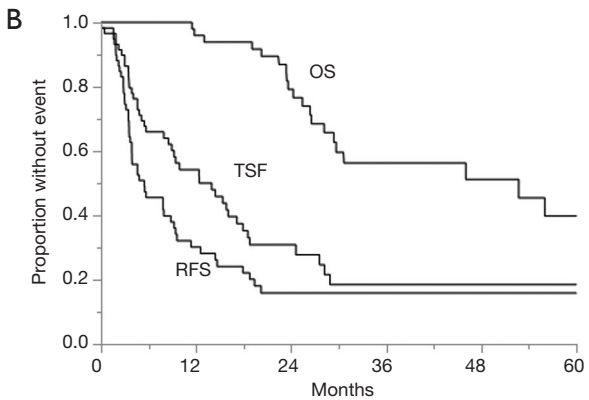
Indeed, there has been no evidence regarding the optimal treatment approach for *RAS*-mutated CLMs. However, repeated resection seems to have survival benefit in both the *RAS* wild cases and *RAS* mutant cases because time-to-surgical failure (45) showed better correlation with overall survival than RFS regardless of the *RAS* mutations status (*Figure 4*). As such, aggressive surgical approach would be the only reliable strategy to maximize survival outcomes of patients with CLM irrespective of *RAS* mutational status.

Conclusions

RAS mutation is reportedly associated with oncological aggressiveness of CLMs especially with higher risk of lung metastases which precludes curative-intent treatment and determines time-to-surgical failure. Although there has been scarce evidence that additional treatment such as perioperative chemotherapy is effective for *RAS*-mutated CLMs, aggressive surgical approach seems to improve overall survival through prolonged cancer-free interval regardless of the *RAS* mutational status. Therefore, basic multidisciplinary approach for CLMs would be important



		RFS		TSF	
		Event	Censored	Event	Censored
OS	Event	17	0	17	0
	Censored	37	26	19	44
Concordance proportion		0.538		0.763	



		RFS		TSF	
		Event	Censored	Event	Censored
OS	Event	25	0	25	0
	Censored	22	12	16	18
Concordance proportion		0.627		0.729	

Figure 4 Comparison of survival measures stratified by *RAS* mutational status. (A) RAS wild (n=80); (B) *RAS* mutant (n=59). OS, overall survival; RFS, recurrence-free survival; TSF, time-to-surgical failure.

in both *RAS* wild CLMs and *RAS*-mutated CLMs to maximize survival outcomes.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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