Review Article

Limitations of molecular biomarkers in patients with resectable colorectal liver metastases

Kristoffer W. Brudvik[1], Junichi Shindoh[2]

[1]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [2]Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kristoffer W. Brudvik, MD, PhD. Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, PO Box 4950 Nydalen, 0424 Oslo, Norway. Email: kristoffer@brudvik.dk.

Abstract: Surgeons are exploring the use of molecular biomarkers in patients with colorectal liver metastases (CLM) to improve preoperative prognostication and selection. This is important because surrogate markers of tumor biology remain insufficient to predict clinical outcomes. In the current literature, there is agreement for the association between *RAS* and *BRAF* mutations and poor long-term outcome after hepatectomy. While this knowledge is gradually being implemented in the clinical work-up of patients, their limitations and implications have yet to be fully understood. Recent data indicate that combinations of coexisting mutations may refine the molecular scoring into footprints of good and bad. This already complex information must be interpreted in light of recent understanding of clonal heterogeneity and genetic diversity of colorectal cancer and CLM. In the clinical settings, it is important to approach new insight into molecular biomarkers with caution. However, it is likely that in the future, genomic analysis will determine which patient is amenable to surgery or not, the timing of surgery versus other modalities, as well as how to approach the metastases technically. Here we review current knowledge about molecular biomarkers in the treatment of CLM and the limitations to consider at the translation to clinical practice.

Keywords: Molecular; biomarkers; colorectal; liver; metastases; limitations

Submitted Jun 26, 2019. Accepted for publication Aug 02, 2019.
doi: 10.21037/cco.2019.08.02
View this article at: http://dx.doi.org/10.21037/cco.2019.08.02

Introduction

The reported 5-year overall survival of patients with colorectal liver metastases (CLM) undergoing hepatic resection has increased from 20–30% to 40–50% since early publications in the 1970s (1,2). This is likely due to improvements in surgical management (3,4) and the introduction of modern chemotherapy with a better understanding of patient selection (5). Fifty years ago, surgeons experienced discrepancy between clinicopathological features of tumor and long-term outcomes after resection. While aggressive unresectable recurrence was observed in several patients with small solitary metastasis, long-term survival was observed in a patient group presenting with multiple or large metastases. Although prognostic drivers were unknown, these observations opened for a new aggressive approach for advanced colorectal cancer. With the introduction of new effective chemotherapy, even more aggressive surgeries are performed in the responders (6). However, surgeons are still troubled with a black box which determines the fate of patients, regardless of a multidisciplinary approach (7).

The surgical repertoire for patients with CLM has become extensive. Unresectable disease can no longer be defined by absolute anatomical criteria (8,9). Liver growth through portal flow modulation methods allows

safer resection in patients with insufficient future liver remnant (FLR) (10,11). Vascular reconstruction can expand surgical indication for a disease previously assessed as unresectable (12). Finally, liver transplantation has been performed in a super selected population with unresectable CLM with reported long-term outcome exceeding that of patients with resectable disease (13). In modern series of patients undergoing resection of CLM, roughly one third of the patients experience recurrence within 1 year (14). Another third achieves a "steady state" with prolonged disease-free survival between recurrences of resectable disease. Patients undergoing the 3th and 4th liver resection for recurring disease is not uncommon in modern series, and the survival after each hepatectomy is similar (6). Finally, the last third of patients achieves long-term survival.

Patient selection is still of major interest and a challenge among surgeons treating CLM. Selection to perform surgery is as important as selection not to perform surgery, and is part of the concept of personalized treatment (15). The timing of surgery is also important as a part of selection and considering the phenotype of the tumor biology. With the use of modern chemotherapy and targeted agents, conventional clinicopathological factors may be less important for the purpose of selection (16). Next generation patient selection is likely to incorporate, or be largely based on, molecular markers that may affect tumor biology. Here, we review clinical and genomic limitations regarding the implementation of current molecular markers for clinical decision making in management of patients with resectable CLM.

Clinical significance of RAS mutations in patients with resectable CLM and its limitations

Recently, mutations in the genes of the rat sarcoma viral oncogene homolog (*RAS*) subfamily have gained interest as molecular markers in CLM. The genes, in their wild-type form, acts as a molecular on/off switch in the epidermal growth factor receptor (EGFR) pathway, a mitogenic pathway, and predict response to anti-EGFR treatment. The literature also reports a prognostic role of *RAS* mutations and association between *RAS* mutational status and survival outcomes after resection of CLM (17). It has also been reported that *RAS* mutations may predict poorer response to modern preoperative chemotherapy, even in the cases without anti-EGFR antibodies (18).

One important limitation of these studies was the retrospective nature in which the patients were identified and included in analysis (19-21). The early publications reported data from 60 to 193 patients, representing merely 15% to 30% of the total respective institutional volumes (19-22). Known *RAS* mutation status was a necessity for inclusion, while *RAS* mutation testing was not performed routinely. Targeted anti-EGFR treatment is seldom used perioperatively, and testing may have been performed more often in patients assessed as borderline resectable or initially unresectable tumors. Patients achieving a resectable state after treatment with modern chemotherapy may have caused imbalance towards patients with worse biology in retrospective analyses of the impact of *RAS* mutations. Interestingly, in a number of publications, even the survival among *RAS* wild-type patients was reported inferior to that expected and reported in complete cohorts of resectable patients. As a consequence, it has been questioned whether *RAS* mutations are truly biomarkers for biology or byproducts of patient selection (23). However, in these retrospective studies, *RAS* mutations are still significantly associated with worse outcome compared to *RAS* wild-type. The important point is whether these observations in retrospective studies are generalizable for decision making in actual clinical management of patients with CLM according to *RAS* mutational status.

Prospective studies are now confirming the association between *RAS* mutations and poor outcome after resection of CLM, strengthening the evidence of *RAS* mutations as molecular biomarkers in all patients with resectable CLM (Brunsell TH *et al.* 2019, unpublished data and Berg KCG *et al.* 2019, unpublished data). *RAS* mutations may not hold the same prognostic value in unresectable metastatic colorectal cancer as in resectable CLM (24), but this remains somewhat controversial (25). One possible explanation for the observed difference between unresectable metastatic colorectal cancer and resectable CLM may be the impact of intercurrent prognostic factors in multivariable independency analysis. In unresectable patients, the presence of disease may be a strong driver of prognosis, rendering less powerful factors insignificant in analysis. This is likely similar for the classical clinicopathological factors as for *RAS* mutations.

It has been hypothesized that *RAS*-mutated metastases have a more aggressive growth pattern than *RAS* wild-type metastases (26). Investigators have explored this in the context of an unfree resection margin after resection, higher rates of local recurrence after ablation, and survival after reresection (27-29). All outcomes were found negatively associated with *RAS*-mutated metastases. Whether these findings can be explained by a more invasive

and migratory tumor biology of the mutated metastases, or this finding could be a result of poorer response to preoperative chemotherapy or any other factor, remains uncertain. One study described a shorter median resection margin in *RAS*-mutated CLM irrespective of the size of the metastases and discussed theories of different types of tumor growth and microscopic tumor deposit (27). Another study found anatomic resection may be better than non-anatomic resection for *RAS*-mutated CLM to clear a larger margin (30). However, the molecular impact on growth pattern, micrometastases, and tumor microenvironment should be approached with caution in studies powered and designed for a clinical outcome. Furthermore, while *RAS* mutations may be associated with recurrence, the intrahepatic site of the recurrence is poorly described. Parenchymal sparing liver resection, when possible, is still recommended to allow for reresections (31,32).

There are subfamilies of the *RAS* gene. *KRAS* is the most common, typically detected in 20% to 50% of colorectal metastases upon resection. *NRAS* is less common and usually present in less than 5% (19). The subfamilies are regulated similarly, but their proteins likely to act at different locations within the cell. There are publications suggesting all *RAS* mutations should be assessed similarly (33) and have the same impact on outcome. However, there has been no solid conclusion because of the low frequency of these mutations. Furthermore, in colorectal cancer, mutations in the *RAS* genes most commonly occur in codons 12, 13, 61 and 146. Investigators have suggested different impacts on survival for the different codon mutations (34), but this finding could not be validated in another patient cohort and therefore remains uncertain (35).

Clinical significance of BRAF mutations in patients with resectable CLM and its limitations

BRAF mutations occur in 7% to 10% of metastatic colorectal cancer. In cohorts of patients with resectable metastatic disease, often less than 5% have *BRAF* mutations, which is likely a result of selection (36). Due to the low frequency of these mutations, it has been difficult to perform retrospective or prospective analysis to determine the impact on outcome, but *BRAF* mutations have been associated with poor survival after resection of CLM. *BRAF*-mutated tumors more often present with peritoneal metastases, and it could be that the biology of the disease renders the patients less likely candidates for liver resection (37). Other studies, however, found less extrahepatic disease in *BRAF*-mutated tumors (36).

While most previous studies have highlighted significantly worse survival of patients with *BRAF* mutations, emerging evidence has suggested that there seem to be several groups of patients presenting acceptable clinical outcomes even with *BRAF*-mutated status. Recently, a case-matched comparison was performed between *BRAF* wild and *BRAF*-mutated CLM using a large cohort from 24 centers. The researchers found that surgical treatment for resectable *BRAF*-mutated CLM was not associated with increased risk of recurrence compared with those with wild type *BRAF*, but *BRAF* mutation was associated with worse survival after development of recurrence (38). Another study has reported that while *BRAF* V600E mutations were associated with worse survival outcomes in general, patients with deficient mismatch repair tumor and/or resectable disease experienced a longer survival than expected (39). A large cohort study from China also confirmed that *BRAF* mutation was not associated with worse survival in stage I–III colorectal cancer, while it was an independent prognostic factor in stage IV colorectal cancer (40). As such, although *BRAF* mutation could be an independent prognostic factor, there has been no sufficient evidence for precluding surgery for *BRAF*-mutated CLMs, and aggressive multidisciplinary treatment approach remains a mainstay regardless of the mutational status in *BRAF*.

From single mutation to molecular footprints in resectable CLM

Despite extensive efforts to investigate molecular drivers that determine the fate of patients with CLM in actual clinical settings, no single molecular biomarker has been found to be suitable for excluding patients with CLM from liver resection. Because the overall picture of oncological molecular status seems to be complex and not well understood so far, it remains difficult to base clinical decisions entirely on this data in patients with CLM. Recently, several groups have reported that combination of mutational status in several molecular markers may better predict clinical outcomes of patients with CLM (41-45). Kawaguchi *et al.* reported the clinical impact of coexisting mutations in *RAS*, *TP53*, and *SMAD4* and showed that *RAS* mutation status alone is not sufficient for precisely predicting prognosis after CLM resection (46).

In addition to these conventional viewpoints regarding the molecular status in tumor tissue, Nishioka *et al.* has recently reported that genetic background of the host

could also be a new prognostic marker for CLM (47). In a comprehensive screening of 578 cancer-related genes, they found that *MICA* variant, an MHC class I chain-related gene family which is associated with innate immune response, shows significant correlation with response to chemotherapy and recurrence-free survival after CLM resection. Because somatic mutation is quite rare in the *MICA* gene and very high concordance rate was confirmed between the normal liver tissue and tumors, these results suggest that immune profiles in each host could be a new target of research in the field of biomarkers of CLM. However, we are still at the entrance of the vast genetic and molecular backgrounds of CLMs. Further studies are needed to define an optimal combination of genes to be screened for clinical management.

Spatiotemporal heterogeneity in patients with resectable CLM

It has been reported that clonal heterogeneity and genetic diversity exist within the same colorectal cancer sample (i.e., intratumoral heterogeneity) (48). Del Carmen *et al.* investigated mutational profiles in primary tumors, lymph nodes and liver metastases from 26 untreated metastatic colorectal cancer patients and confirmed the presence of different mutational profiles among primary tumors, lymph node metastases and liver metastases (49). These findings are clinically important because both intratumoral and intertumoral heterogeneity could affect the response to targeted therapies.

Routine clinical *RAS* testing is performed by Sanger sequencing or polymerase chain reaction. With such conventional methods, however, it is difficult to identify spatial heterogeneity of tumor (i.e., intratumoral or intertumoral heterogeneity) or genetic profile alterations that are usually caused by anticancer agents (temporal heterogeneity) during the clinical course. Therefore, more sophisticated, sensitive tests including liquid biopsy and a strategy to screening the refractory nature of tumors would be needed to better characterize tumor biology and alter clinical management as appropriate.

Impact of treatment on molecular profiles of cancer

With introduction of modern chemotherapy and multidisciplinary treatment, traditional clinicopathological factors are losing their weight in prediction of prognostic outcomes (16). For example, response to chemotherapy may be more important than size and number of CLM. Synchronous CLM responding to preoperative chemotherapy may prognostically be in a better place than metachronous CLM emerging after adjuvant chemotherapy for primary lesion. Also, *RAS* mutation is a potent prognostic factor as we discussed earlier.

Importantly, use of chemotherapy might provide a selection pressure. One study reported that the mutational status of *KRAS* may not be altered by treatment with oxaliplatin-based modern chemotherapy (50), while another study reported higher rates of somatic gene mutations in metachronous CLM after oxaliplatin based adjuvant treatment for the primary colorectal cancer (51). These results suggest that modern chemotherapy may prevent recurrence in *KRAS* wild-type patients, favoring chemotherapy-resistant *KRAS*-mutated subsets to form recurrence.

Similar concepts could be applied in the setting of preoperative chemotherapy. Given that complete removal of cancerous tissue may provide a chance of cure even for a patient with stage IV colorectal cancer, the goal of preoperative chemotherapy may not be cytoreduction of tumor. An important purpose of preoperative chemotherapy is, instead, improved selection of patients who will truly benefit from surgery. Single somatic mutations do not dictate the full phenotype of a tumor, thus preoperative observation under chemotherapy may offer important information on tumor biology and curative potential of patients, regardless of known biologic markers including *RAS* mutational status.

Conclusions

Increased knowledge about molecular biomarkers and understanding of tumor biology may explain differences between the expected and the observed outcome after resection of CLM. This information is important for surgeons as this may aid better patient selection and surgery. However, we are only in the early days of understanding how to use this information in clinical decision making.

Each newly proposed molecular biomarker should be validated in prospective patient series to reduce the risk of selection bias. Furthermore, when expanding the panel of molecular biomarkers available in resectable CLM, parallel research should be aimed to explain molecular mechanisms and how the data can be translated to clinically meaningful information (52).

Personalized medicine will continue to evolve, especially in the field of medical oncology, but also in surgical oncology. Molecular biomarkers are included in the overall assessment of patients before resection of CLM. So far, no biomarker has been found suited to exclude patients from surgery, and selection to surgery is still largely based on personal judgement by the surgeons. While it is important to approach new information about molecular biomarkers with caution, it is likely that in the future, genomic analysis will determine which patient is amenable to surgery or not, the timing of surgery versus other modalities, as well as how to approach the metastases technically.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

References

1. Wilson SM, Adson MA. Surgical treatment of hepatic metastases from colorectal cancers. Arch Surg 1976;111:330-4.
2. Vigano L, Russolillo N, Ferrero A, et al. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. Ann Surg Oncol 2012;19:2035-44.
3. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198-206; discussion 1206.
4. Day RW, Brudvik KW, Vauthey JN, et al. Advances in hepatectomy technique: Toward zero transfusions in the modern era of liver surgery. Surgery 2016;159:793-801.
5. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg 2004;240:1052-61; discussion 1061-4.
6. Brudvik KW, Bains SJ, Seeberg LT, et al. Aggressive treatment of patients with metastatic colorectal cancer increases survival: a scandinavian single-center experience. HPB Surg 2013;2013:727095.
7. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? Ann Surg 2007;246:183-91.
8. Yamamoto M, Akamatsu N, Hayashi A, et al. Safety and efficacy of venous reconstruction in liver resection using cryopreserved homologous veins. J Hepatobiliary Pancreat Sci 2017;24:511-9.
9. Hemming AW, Reed AI, Langham MR, et al. Hepatic vein reconstruction for resection of hepatic tumors. Ann Surg 2002;235:850-8.
10. Kawaguchi Y, Lillemoe HA, Vauthey JN. Dealing with an insufficient future liver remnant: Portal vein embolization and two-stage hepatectomy. J Surg Oncol 2019;119:594-603.
11. Sandstrom P, Rosok BI, Sparrelid E, et al. 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;267:833-40.
12. Berumen J, Hemming A. Vascular Reconstruction in Hepatic Malignancy. Surg Clin North Am 2016;96:283-98.
13. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257:800-6.
14. Jones RP, Jackson R, Dunne DF, et al. Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases. Br J Surg 2012;99:477-86.
15. Dienstmann R, Salazar R, Tabernero J. Personalizing colon cancer adjuvant therapy: selecting optimal treatments for individual patients. J Clin Oncol 2015;33:1787-96.
16. Brudvik KW, Jones RP, Giuliante F, et al. RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases. Ann Surg 2019;269:120-6.
17. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg 2015;102:1175-83.
18. Zimmitti G, Shindoh J, Mise Y, et al. RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy before resection of colorectal liver metastases. Ann Surg Oncol 2015;22:834-42.
19. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 2013;258:619-26; discussion 626-7.
20. Karagkounis G, Torbenson MS, Daniel HD, et al. Incidence and prognostic impact of KRAS and BRAF

mutation in patients undergoing liver surgery for colorectal metastases. Cancer 2013;119:4137-44.
21. Kemeny NE, Chou JF, Capanu M, et al. KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. Cancer 2014;120:3965-71.
22. Stremitzer S, Stift J, Gruenberger B, et al. KRAS status and outcome of liver resection after neoadjuvant chemotherapy including bevacizumab. Br J Surg 2012;99:1575-82.
23. Søreide K, Sandvik OM, Søreide JA. KRAS mutation in patients undergoing hepatic resection for colorectal liver metastasis: a biomarker of cancer biology or a byproduct of patient selection? Cancer 2014;120:3862-5.
24. Bruera G, Cannita K, Di Giacomo D, et al. Prognostic value of KRAS genotype in metastatic colorectal cancer (MCRC) patients treated with intensive triplet chemotherapy plus bevacizumab (FIr-B/FOx) according to extension of metastatic disease. BMC Med 2012;10:135.
25. Liang L, Tian J, Yu Y, et al. An Analysis of Relationship Between RAS Mutations and Prognosis of Primary Tumour Resection for Metastatic Colorectal Cancer Patients. Cell Physiol Biochem 2018;50:768-82.
26. Pollock CB, Shirasawa S, Sasazuki T, et al. Oncogenic K-RAS is required to maintain changes in cytoskeletal organization, adhesion, and motility in colon cancer cells. Cancer Res 2005;65:1244-50.
27. Brudvik KW, Mise Y, Chung MH, et al. RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases. Ann Surg Oncol 2016;23:2635-43.
28. Odisio BC, Yamashita S, Huang SY, et al. Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status. Br J Surg 2017;104:760-8.
29. Okuno M, Goumard C, Kopetz S, et al. RAS Mutation is Associated with Unsalvageable Recurrence Following Hepatectomy for Colorectal Cancer Liver Metastases. Ann Surg Oncol 2018;25:2457-66.
30. Margonis GA, Buettner S, Andreatos N, et al. Anatomical Resections Improve Disease-free Survival in Patients With KRAS-mutated Colorectal Liver Metastases. Ann Surg 2017;266:641-9.
31. Mise Y, Aloia TA, Brudvik KW, et al. Parenchymal-sparing Hepatectomy in Colorectal Liver Metastasis Improves Salvageability and Survival. Ann Surg 2016;263:146-52.
32. Kazaryan AM, Aghayan DL, Barkhatov LI, et al. Laparoscopic Multiple Parenchyma-sparing Concomitant Liver Resections for Colorectal Liver Metastases. Surg Laparosc Endosc Percutan Tech 2019;29:187-93.
33. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34.
34. Margonis GA, Kim Y, Spolverato G, et al. Association Between Specific Mutations in KRAS Codon 12 and Colorectal Liver Metastasis. JAMA Surg 2015;150:722-9.
35. Passot G, Denbo JW, Yamashita S, et al. Is hepatectomy justified for patients with RAS mutant colorectal liver metastases? An analysis of 524 patients undergoing curative liver resection. Surgery 2017;161:332-40.
36. Gagnière J, Dupré A, Gholami SS, et al. Is Hepatectomy Justified for BRAF Mutant Colorectal Liver Metastases?: A Multi-institutional Analysis of 1497 Patients. Ann Surg 2018. [Epub ahead of print].
37. Yaeger R, Cercek A, Chou JF, et al. BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. Cancer 2014;120:2316-24.
38. Bachet JB, Moreno-Lopez N, Vigano L, et al. BRAF mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases. Br J Surg 2019;106:1237-47.
39. de la Fouchardière C, Cohen R, Malka D, et al. Characteristics of BRAF V600E Mutant, Deficient Mismatch Repair/Proficient Mismatch Repair, Metastatic Colorectal Cancer: A Multicenter Series of 287 Patients. Oncologist 2019. [Epub ahead of print].
40. Guo TA, Wu YC, Tan C, et al. Clinicopathologic features and prognostic value of KRAS, NRAS and BRAF mutations and DNA mismatch repair status: A single-center retrospective study of 1,834 Chinese patients with Stage I-IV colorectal cancer. Int J Cancer 2019;145:1625-34.
41. Chun YS, Passot G, Yamashita S, et al. Deleterious Effect of RAS and Evolutionary High-risk TP53 Double Mutation in Colorectal Liver Metastases. Ann Surg 2019;269:917-23.
42. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.
43. Kawaguchi Y, Lillemoe HA, Panettieri E, et al. Conditional Recurrence-Free Survival after Resection of Colorectal Liver Metastases: Persistent Deleterious Association with RAS and TP53 Co-Mutation. J Am Coll Surg 2019. [Epub ahead of print].
44. Mizuno T, Cloyd JM, Vicente D, et al. SMAD4 gene mutation predicts poor prognosis in patients undergoing resection for colorectal liver metastases. Eur J Surg Oncol

2018;44:684-92.
45. Yamashita S, Chun YS, Kopetz SE, et al. APC and PIK3CA Mutational Cooperativity Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colorectal Liver Metastases. Ann Surg 2017. [Epub ahead of print].
46. Kawaguchi Y, Kopetz S, Newhook TE, et al. Mutation Status of RAS, TP53, and SMAD4 is Superior to Mutation Status of RAS Alone for Predicting Prognosis after Resection of Colorectal Liver Metastases. Clin Cancer Res 2019. [Epub ahead of print].
47. Nishioka Y, Shindoh J, Inagaki Y, et al. Host MICA Polymorphism as a Potential Predictive Marker in Response to Chemotherapy for Colorectal Liver Metastases. Dig Dis 2018;36:437-45.
48. Sayagues JM, Abad Mdel M, Melchor HB, et al. Intratumoural cytogenetic heterogeneity of sporadic colorectal carcinomas suggests several pathways to liver metastasis. J Pathol 2010;221:308-19.
49. Del Carmen S, Sayagues JM, Bengoechea O, et al. Spatio-temporal tumor heterogeneity in metastatic CRC tumors: a mutational-based approach. Oncotarget 2018;9:34279-88.
50. Kawamoto Y, Tsuchihara K, Yoshino T, et al. KRAS mutations in primary tumours and post-FOLFOX metastatic lesions in cases of colorectal cancer. Br J Cancer 2012;107:340-4.
51. Andreou A, Kopetz S, Maru DM, et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. Ann Surg 2012;256:642-50.
52. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35:1453-86.

Cite this article as: Brudvik KW, Shindoh J. Limitations of molecular biomarkers in patients with resectable colorectal liver metastases. Chin Clin Oncol 2019;8(5):48. doi:10.21037/cco.2019.08.02