Maximum Diameter and Number of Tumors as a New Prognostic Indicator of Colorectal Liver Metastases

TOSHIAKI YOSHIMOTO, YUJI MORINE, SATORU IMURA, TETSUYA IKEMOTO, SYUICHI IWAHASHI,
YU SAITO, SINICHIRO YAMADA, DAICHI ISHIKAWA, HIROKI TERAOKU,
MASATO YOSHIKAWA, JUN HIGASHIJIMA, CHIE TAKASU and MITSUO SHIMADA

Department of Surgery, The University of Tokushima Graduate School, Tokushima, Japan

Abstract. *Background: Surgical resection is currently considered the only potentially curative option as a treatment strategy of colorectal liver metastases (CRLM). However, the criteria for selection of resectable CRLM are not clear. The aim of this study was to confirm a new prognostic indicator of CRLM after hepatic resection. Patients and Methods: One hundred thirty nine patients who underwent initial surgical resection from 1994 to 2015 were investigated retrospectively. Prognostic factors of overall survival including the product of maximum diameter and number of metastases (MDN) were analyzed. Results: Primary tumor differentiation, vessel invasion, lymph node (LN) metastasis, non-optimally resectable metastases, H score, grade of liver metastases, resection with non-curative intent and MDN were found to be prognostic factors of overall survival (OS). In multivariate analyses of clinicopathological features associated with OS, MDN and non-curative intent were independent prognostic factors. Patients with MDN ≥30 had shown significantly poorer prognosis than patients with MDN <30 in OS and relapse-free survival (RFS). Conclusion: MDN ≥30 is an independent prognostic factor of survival in patients with CRLM and optimal surgical criterion of hepatectomy for CRLM.*

The liver is the most common site of metastasis in patients with colorectal cancer (CRC) (1), with 15-25% of patients presenting synchronous colorectal liver metastases (CRLM) (2). In addition, another 25-50% of patients develop subsequent metachronous metastases during the course of the disease (2, 3). Surgical resection is currently considered the

only potentially curative option for patients with metastatic CRC confined to the liver (4, 5), and is associated with a 5-year overall survival (OS) rate of 37-58% (6). However, only 15-30% of patients with liver metastases may be initially resectable (7, 8), but the criteria for selection of resectable CRLM remain unclear.

According to Nordlinger *et al.*, patients with CRLM have been classified into three clinical categories: (i) patients with resectable metastatic disease; (ii) patients with metastatic disease that is not optimally resectable (tumor size >5 cm, >4 metastases, synchronous CRLM, primary lymph node (LN)-positive, positive tumor markers and/or technically difficult) and (iii) patients unlikely to ever become resectable (9). Neoadjuvant chemotherapy was recommended for patients with resectable and unresectable CRLM, whereas first-line surgical resection was recommended only for patients with solitary metastases ≤2 cm and good prognostic features (10). In the European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with CRLM, patients were categorized by technical and oncological criteria. Oncological categories include (i) concomitant extrahepatic disease; (ii) number of lesions ≥5; (iii) tumor progression, with no mention of tumor size (11). However, clear criteria of surgical resection for CRLM have never been established.

On the other hand, in hepatocellular carcinoma, the Milan criteria are used for a simple selection for liver transplantation around the world. The adaptation of liver transplantation was limited to one lesion smaller than 5 cm or up to 3 lesions smaller than 3 cm, and it is representing an approximate volume of tumor. In CRLM, simple criteria, using tumor number and size are required.

Perioperative or neoadjuvant chemotherapy with various agents, alone or in combination, is the standard of care for most patients with CRLM (12, 13). Neoadjuvant chemotherapy in patients with initially unresectable CRLM can reduce metastasis sizes, converting initially unresectable to resectable lesions (conversion treatment) (9), making systemic chemotherapy in combination with liver resection an accepted

standard of care in patients with CRLM (10, 14). However, there are currently no particular criteria for resectability of CRLM, especially focusing on tumor volume in the liver.

The aim of this study was to confirm a new prognostic indicator of CRLM after hepatic resection.

Patients and Methods

Patients. This study was performed in accordance with the Helsinki Declaration of the World Medical Association. This retrospective study enrolled 246 patients with CRLM treated at Tokushima University Hospital from 1994 to 2015. Of these, 139 patients who underwent initial surgical resection with curative intent and without any preceding chemotherapy were included in this study. The remaining patients included 22 who received best supportive care and 85 who received systemic chemotherapy. Our treatment strategy for CRLM is curative hepatectomy whenever possible on all patients with CRLM if their remnant liver volume was ≥40%, even after chemotherapy or hepatectomy.

Patients were evaluated preoperatively by abdominal ultrasound (US), helical computed tomography (CT) scan, and/or magnetic resonance imaging (MRI). All with CRC and synchronous or metachronous liver metastases were diagnosed histologically. Maximum tumor diameter and number of tumors were determined by CT and resected specimen. Resection status (curative *vs*. non-curative) was evaluated by histopathological assessment of excised metastases together with the operation notes.

The 139 patients included 85 men and 54 women with mean age 66±0.95 years (range=33-92 years). The median patient follow-up for all patients was 48.7 months (range=4.4-162.1 months). Perioperative mortality was defined as death within 3 months of operation. In all 139 patients who underwent initial hepatic resection, the perioperative mortality was 0%.

Methods. Staging and curability were defined according to the criteria of the Japanese Society for Cancer of the Colon and Rectum. Liver metastasis was classified as H1–3, with H1 defined as four or fewer tumors with a maximum diameter <5 cm; H3 as >5 tumors of size >5 cm; and H2 as anything intermediate. Liver metastasis grade was defined as A-C, with H1 and ≤3 regional LN metastases classified as grade A; H2 with ≤3 regional LN metastases or H1 with ≥4 LN metastases classified as grade B, and all other conditions classified as grade C.

Statistical analysis. Univariate analysis of differences between groups was determined by log-rank tests and multivariate analysis by chi-squared tests. The endpoints were overall survival (OS) and relapse-free survival (RFS). Survival curves were plotted using the Kaplan–Meier method and 5-year OS and RFS rates were analyzed. Two-sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using JMP version 13 statistical software (SAS, Campus Drive Cary, NC, USA).

Results

Overall and relapse-free survival. Survival curves of the 139 patients were plotted by the Kaplan–Meier method. The 5-year OS and RFS rates were 58.9% and 26.8%, respectively (Figure 1). Median overall survival was 89.26 months (SD=2.92).
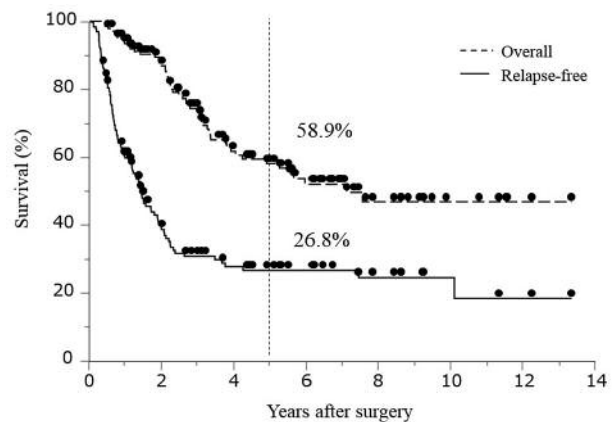

Figure 1. *Overall and relapse-free survival curves of 139 patients with colorectal liver metastases who underwent initial surgical resection.*

Univariate and multivariate analysis of clinicopathological features associated with overall survival. The product of maximum diameter and number (MDN) was newly defined as an indicator of tumor volume (or amount) in the liver. Table I shows univariate analyses of clinicopathological features associated with OS. Primary tumor differentiation (*p*<0.0001), vessel invasion (*p*=0.0458) and LN metastasis (*p*=0.0089) were significantly prognostic of 5-year OS. Moreover, non-optimally resectable metastases (*p*=0.0236), H score (*p*=0.0265), grade of liver metastases (*p*=0.0005), resection with non-curative intent (*p*=0.0017), and MDN (*p*=0.0006) were metastatic factors significantly prognostic for OS. Table II shows multivariate analyses of clinicopathological features associated with OS. MDN (*p*=0.0145) and non-curative intent (*p*=0.0451) were independently prognostic of survival in this patient cohort.

Relationships of MDN to OS and RFS rates. Figure 2a shows the Kaplan-Meier OS and RFS curves for these patients after initial hepatic resection. Patients with MDN ≥30 had significantly poorer prognosis than those with MDN <30, with 5-year OS rates of 23.4% and 63.7%, respectively (*p*=0.0006; Figure 2a). MDN was also significantly prognostic of RFS, with patients with MDN ≥30 having significantly poorer prognosis than those with MDN <30 (*p*=0.018; Figure 2b).

Discussion

CRLM may present synchronously in 15-25% of CRC patients, with an additional 30% developing metastases during the course of the disease. Hepatic resection is the only potentially curative treatment for CRLM and may improve patient prognosis (15). Although approximately 20% of patients have potentially resectable metastases and a better

Table I. *Association between clinicopathological features and 5-year overall survival (OS) rates in patients who underwent surgical resection for colorectal liver metastases (CRLM).*

Factors		5-year OS (%)	*p*-Value
Age	≤65/>65	56.0/62.2	0.4691
Gender	M/F	64.3/50.5	0.1543
Metastasis Period	Synchronous/metachronous	50.2/68.1	0.1081
CEA	≤50 ng/ml/>50 ng/ml	58.8/65.0	0.2362
CA19-9	≤100 U/ml/>100 U/ml	66.3/32.7	0.0850
Primary site			
Location	Colon/rectum	63.5/52.5	0.2427
Differentiation	tub/poor	58.7/0	<0.0001
Lymphatic invasion	-/+	66.7/53.5	0.6869
Vessel invasion	-/+	67.2/53.7	0.0458
LN metastasis	-/+	72.7/48.9	0.0089
Metastatic site			
Non-optimally	-/+	78.7/48.6	0.0236
H	H1/H2, 3	64.1/47.6	0.0265
Grade	A/B, C	72.9/42.5	0.0005
Maximum diameter	<5 cm/>5 cm	60.9/51.1	0.2049
Number of tumors	<5/ >5	62.6/46.0	0.1380
MDN	<30/ >30	62.9/23.4	0.0006
Curative intent	Cur./non-Cur.	60.5/0	0.0017
Neoadjuvant	-/+	57.9/59.7	0.5199
Adjuvant	-/+	61.2/57.9	0.6285

MDN: Maximum diameter × number.

chance of long-term survival (16), there is no definitive criteria for selection of resectable CRLM. Thus, defining resectable CRLM and developing treatment strategies are crucially important.

In Japan, there are five criteria for hepatectomy in patients with CRLM: (i) patient ability to tolerate surgery; (ii) primary tumor control or possibility of control; (iii) ability to completely resect the metastatic liver tumor; (iv) absence or possibility of control of extrahepatic metastases; and (v) adequate function of the remaining liver (17). CRLM treatment strategies in Japan do not limit tumor number or size.

Previous reports have shown that the number of tumors, largest tumor diameter, LN metastases of the primary tumor, CA19-9 concentration before hepatic resection and extrahepatic metastatic disease were predictive factors of survival after surgical resection of CRLM (15). These factors resulted in a nomogram prediction of disease-free survival following hepatic resection in patients with CRLM (18), but it was complicated in clinical use because of many risk factors.

Regarding to tumor number or size of CRLM, a previous report showed that the presence of ≥3 tumors and tumor size >8 cm (19) and >10 cm (20), as well as ≥1 tumor and tumor size >5 cm (21), were negatively prognostic of OS. Other studies have reported that the presence of ≥3 tumors and tumor size >5 cm (22) and the presence of ≥4 tumors and tumor size >5 cm (23) were negatively prognostic. However,

Table II. *Multivariate analysis of factors associated with 5-year overall survival (OS) rates in patients who underwent surgical resection of colorectal liver metastases (CRLM).*

Factors		Odds ratio (95% CI)	*p*-Value
Primary site			
Differentiation	Poor	6.428 (0.833-134.207)	0.0762
Vessel invasion	+	1.167 (0.481-2.799)	0.7291
LN metastasis	+	2.029 (0.764-5.777)	0.1578
Metastatic site			
Non-optimally	+	1.452 (0.484-4.527)	0.5074
H	2, 3	1.590 (0.397-6.591)	0.5119
Grade	B, C	2.289 (0.661-8.014)	0.1886
MDN	>30	6.503 (1.432-37.232)	0.0145
Curative intent	non-Cur.	4.082 (1.818-9.174)	0.0451

MDN: Maximum diameter × number.

the significance of the dimensions of metastatic lesions as prognostic factors in CRLM surgery is controversial. Indeed, two independent studies found that the dimensions of metastases were not associated with local recurrence or 5-year survival rates (24, 25). Thus, only the dimensions of metastases cannot be considered an exclusion criterion for surgery, unless they compromise the resection margins or the residual functional parenchyma (24).
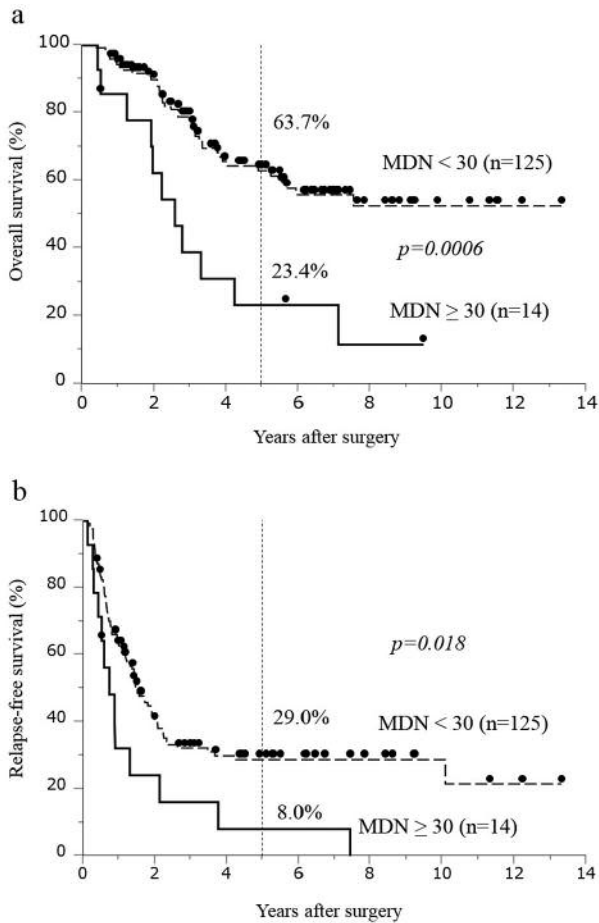
Figure 2. *Kaplan–Meier curves for (a) overall survival and (b) relapse-free survival in patients with colorectal liver metastases (CRLM) of MDN ≥30 and <30.*

On the other hand, in the HCC, The Milan criteria limited the adaptation of liver transplantation to one lesion smaller than 5 cm or up to 3 lesions smaller than 3cm, and it is representing an approximate volume of tumor. Even in the CRLM, simple criteria for resectability especially focusing on tumor volume are required.

In regards to limit of hepatic resection, our institution is most aggressive in the world. In our department, curative hepatectomy was performed whenever possible on patients with CRLM, if the remnant liver volume was ≥40%, even after chemotherapy or hepatectomy. In the criteria of the Japanese Society for Cancer of the Colon and Rectum, H3 liver metastasis was defined as >5 tumors and maximum diameter >5 cm. H3 liver metastasis was judged as not optimally resectable, but it corresponds to MDN ≥25. However, under the condition of aggressive hepatectomy, this study showed that MDN ≥30 was the independent and

strong prognostic factor of OS in patients with CRLM who underwent initial hepatectomy.

Based on these results, our department has devised a treatment strategy, in which patients with CRLM, MDN <30 and remnant liver volume ≥40% undergo hepatectomy, whereas those with MDN ≥30 and/or remnant liver volume <40% receive chemotherapy. Patients regarded as non-optimally resectable are treated with FOLFOXIRI plus Bevacizumab, with those showing a sufficient response undergoing subsequent liver resection.

In conclusion, this study showed that MDN was an independent prognostic factor of survival in patients with CRLM. MDN <30 is the optimal surgical criterion of hepatectomy for CRLM.

References

1 Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D and Adam R: Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol *26(4)*: 702-708, 2015.

2 Lam VW, Pang T, Laurence JM, Johnston E, Hollands MJ, Pleass HC and Richardson AJ: A systematic review of repeat hepatectomy for recurrent colorectal liver metastases. J Gastrointest Surg *17(7)*: 1312-1321, 2013.

3 Lam VW, Laurence JM, Johnston E, Hollands MJ, Pleass HC and Richardson AJ: A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. HPB *15(7)*: 483-491, 2013.

4 Umehara M, Umehara Y, Takahashi K, Murata A, Nishikawa S, Matsuzaka M, Tanaka R and Morita T: Preoperative Chemotherapy with Bevacizumab Extends Disease-free Survival After Resection of Liver Metastases from Colorectal Cancer. Anticancer research *36(4)*: 1949-1954, 2016.

5 Saied A, Katz SC and Espat NJ: Regional hepatic therapies: an important component in the management of colorectal cancer liver metastases. Hepatobiliary Surg Nutr *2(2)*: 97-107, 2013.

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

7 Veereman G, Robays J, Verleye L, Leroy R, Rolfo C, Van CE, Bielen D, Ceelen W, Danse E and De Man M: Pooled analysis of the surgical treatment for colorectal cancer liver metastases. Crit Rev Oncol Hematol *94(1)*: 122-135, 2015.

8 Sabanathan D, Eslick GD and Shannon J: Use of Neoadjuvant Chemotherapy Plus Molecular Targeted Therapy in Colorectal Liver Metastases: A Systematic Review and Meta-analysis. Clin Colorectal Cancer *15(4)*: 141-147, 2016.

9 Nordlinger B, Van CE, Rougier P, Köhne CH, Ychou M, Sobrero A, Adam R, Arvidsson D, Carrato A and Georgoulias V: Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer *43(14)*: 2037-2045, 2007.

10 Nordlinger B, Van CE, Gruenberger T, Glimelius B, Poston G, Rougier P, Sobrero A and Ychou M: Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol *20(6)*: 985-992, 2009.

11 Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Köhne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S and Cervantes A: ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol *23(10)*: 2479-2516, 2012.

12 Brandi G, De Lorenzo S, Nannini M, Curti S, Ottone M, Dall'Olio FG, Barbera MA, Pantaleo MA and Biasco G: Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. World J Gastroenterol *22(2)*: 519-533, 2016.

13 Pietrantonio F, Orlandi A, Inno A, Da Prat V, Spada D, Iaculli A, Di Bartolomeo M, Morosi C and De Braud F: Bevacizumab-based neoadjuvant chemotherapy for colorectal cancer liver metastases: Pitfalls and helpful tricks in a review for clinicians. Crit Rev Oncol Hematol *95(3)*: 272-281, 2015.

14 Khoo E, O'Neill S, Brown E, Wigmore SJ and Harrison EM: Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. HPB *18(6)*: 485-493, 2016.

15 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin *61(2)*: 69-90, 2011.

16 Donadon M, Ribero D, Morris SG, Abdalla E and Vauthey N: New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res *1(1)*: 20-27, 2007.

17 Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Igarashi M and Ishida H: Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol *20(2)*: 207-239, 2015.

18 Toru B, Yoshihiro S, Kiyoshi H, Goro H, Kuniya T, Yoshihito K, Hiroyuki N, Hiroyuki Y, Etsuro H, Masaki U, Hiroyuki T, Hideo B, Tomoo K, Norihiro K, Keiichi T, Itaru E, Go W, Masaru M, Shinji U, Tetsuo O, Ken K, Hiroki Y, Masakazu Y and Tadahiro T: A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci *19(1)*: 72-84, 2012.

19 Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA, Gayowski TJ, Fung JJ and Starzl TE: Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg *189(3)*: 291-299, 1999.

20 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F and Ghémard O: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg *240(4)*: 644-658, 2004.

21 Fong Y, Fortner J, Sun RL, Brennan MF and Blumgart LH: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg *230(3)*: 309-318, 1999.

22 Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A and Mentha G: Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Anna Surg *241(5)*: 715-724, 2005.

23 Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P and Jaeck D: Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer *77(7)*: 1254-1262, 1996.

24 Serrablo A, Paliogiannis P, Pulighe F, Moro SS, Borrego EV, Attene F, Scognamillo F and Hörndler C: Impact of novel histopathological factors on the outcomes of liver surgery for colorectal cancer metastases. Eur J Surg Oncol *42(9)*: 1268-1277, 2016.

25 Elias D, Cavalcanti A, Sabourin JC, Pignon JP, Ducreux M and Lasser P: Results of 136 curative hepatectomies with a safety margin of less than 10 mm for colorectal metastases. J Surg Oncol *69(2)*: 88-93, 1998.