



Prognostic significance of histological categorization of desmoplastic reaction in colorectal liver metastases

Tadakazu Ao¹ · Yoshiki Kajiwara¹ · Keisuke Yonemura¹ · Eiji Shinto¹ · Satsuki Mochizuki¹ · Koichi Okamoto¹ · Suefumi Aosasa¹ · Hideki Ueno¹

Received: 15 February 2019 / Revised: 9 April 2019 / Accepted: 23 April 2019 / Published online: 10 May 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Desmoplastic reaction (DR) involves the growth of fibrous or connective tissues around a tumor and has recently attracted attention as an indicator of malignant potential. Previous studies have confirmed that histological categorization of DR in the primary tumor is an independent prognostic factor in patients with colorectal liver metastases (CRLM). However, it remains unclear whether the DR status of the metastatic liver lesion (DR^{liver}) is a useful prognostic factor. This pathological review evaluated records from 204 patients who underwent hepatectomy for CRLM at the National Defense Medical College Hospital in Japan. Each case's DR^{liver} was classified as mature, intermediate, or immature based on the presence of keloid-like collagen and myxoid stroma in the metastatic liver lesion. This resulted in 12 cases of mature DR^{liver}, 101 cases of intermediate DR^{liver}, and 91 cases of immature DR^{liver}. There was a significant correlation between the DR statuses of the primary tumor and the metastatic liver lesion (Spearman's rho = 0.3, $P = 0.0001$). The 5-year relapse-free survival rates after hepatectomy were 33.8% for mature/intermediate DR^{liver} and 16.7% for immature DR^{liver} ($P = 0.0021$). The 5-year overall survival rate after hepatectomy was higher in the mature/intermediate DR^{liver} group (64.8%) than in the immature DR^{liver} group (35.0%; $P = 0.0012$). The multivariate analysis confirmed that DR^{liver} categorization could independently predict relapse-free survival and overall survival. In conclusion, DR^{liver} categorization may be valuable for predicting prognosis after hepatectomy among patients with CRLM.

Keywords Desmoplastic reaction · Colorectal cancer · Colorectal liver metastases · Cancer-associated fibroblasts · Histopathological prognosticator

Abbreviations

CAF	Cancer-associated fibroblast
CRC	Colorectal cancer
DR	Desmoplastic reaction
DR ^{liver}	Desmoplastic reaction in the colorectal liver metastases
DR ^{primary}	Desmoplastic reaction in the primary tumor
OS	Overall survival
RFS	Relapse-free survival
MLNs	Metastatic lymph nodes

Introduction

Hepatectomy is considered the only effective and potentially curative treatment for patients with colorectal liver metastases (CRLM). However, the 5-year overall survival (OS) rate after hepatectomy is 22–40% and the 10-year OS rate is 20–26% [35]. Moreover, 50–70% of patients experience recurrence after hepatectomy and >30% of patients who undergo curative hepatectomy will experience recurrence within 1 year [4]. Thus, it is important to accurately predict the patient's prognosis after hepatectomy for CRLM, and this prognostication can be based on various quantitative parameters, such as the number of metastases [3, 12, 15, 16, 21], the size of the liver metastasis [3, 15, 25], the presence of extrahepatic disease [3], and primary tumor nodal status [3, 12, 15, 16, 24]. However, only a few reports have considered qualitative parameters, such as the histological growth pattern [33], fibrosis surrounding the liver metastasis [18], and

This article is part of the Topical Collection on *Quality in Pathology*

✉ Yoshiki Kajiwara
ykaji@ndmc.ac.jp

¹ Department of Surgery, National Defense Medical College, 3-2, Namiki, Tokorozawa, Saitama 359-8513, Japan

histological findings for entrapped metastatic liver tumors [11]. These findings have not been applied in clinical practice.

Several recent reports have revealed that histological findings at the invasive front are related to the tumor's behavior and oncological outcomes [28, 29, 37]. In addition, histopathological prognostication for colorectal cancer (CRC) has been attempted based on a novel histological category system that evaluates the desmoplastic reaction (DR), which can be categorized into three patterns (mature, intermediate, and immature) according to the fibrotic stromal components at the invasive front (i.e., hyalinized keloid-like collagen and myxoid stroma). We have reported that the DR categorization in the primary tumor was strongly correlated with prognosis after hepatectomy for CRLM, and that this factor had greater prognostic value than other histological factors, including TNM stage [32]. The formation of DR can also be observed in metastatic lesions, although we are not aware of any reports that have described the value of DR in metastatic liver lesions (DR^{liver}) for predicting prognosis among patients with CRLM. Therefore, this study aimed to determine whether DR^{liver} could be categorized in the same manner as for the primary tumor, and to determine whether this categorization provided prognostic value among patients who underwent hepatectomy for CRLM.

Materials and methods

Patients

This retrospective study evaluated data from 204 patients with CRC who underwent liver resection for synchronous CRLM ($n = 101$) or metachronous CRLM ($n = 103$) at the National Defense Medical College Hospital between 1997 and 2014. The average age was 64.3 years (range, 28–95 years) and 138 patients (67.6%) were men. Based on an average follow-up period of 60 months (range, 1–204 months) for survivors, the 5-year overall survival (OS) rate after hepatectomy was 52.8%. Among the 193 patients who underwent potentially curative hepatectomy, the 5-year relapse-free survival (RFS) rate after hepatectomy was 26.2%. Patients who received chemotherapy within 2 months before the hepatectomy were defined as the preoperative chemotherapy group. Preoperative chemotherapy was administered to 78 patients, which involved oxaliplatin-based regimens (40 patients), irinotecan-based regimens (17 patients), 5-fluorouracil-based regimens (31 patients), other regimens (2 patients), anti-vascular endothelial growth factor (VEGF) antibodies (20 patients), anti-epidermal growth factor receptor (EGFR) antibodies (10 patients), and hepatic intra-arterial chemotherapy (6 patients). Sixty-nine patients received postoperative adjuvant chemotherapy, which involved oxaliplatin-based regimens (17

patients), irinotecan-based regimens (10 patients), 5-fluorouracil-based regimens (39 patients), anti-VEGF antibodies (3 patients), anti-EGFR antibodies (3 patients), and hepatic intra-arterial chemotherapy (6 patients).

Among the 204 cases, the primary tumor could not be evaluated in 44 cases because the patients underwent primary resection at another hospital (38 cases) or the histological specimens had been discarded based on our center's policy regarding specimen storage (6 cases). Thus, pathological reports for the primary tumor were available for 160 patients (151 of the 160 patients had undergone potentially curative liver resection). A single researcher (TA) was blinded to the patients' outcomes and evaluated the pathological findings to determine the DR categories for the CRLM and the primary tumor (when available). This study's protocol was approved by the relevant institutional review board.

Histological categorization of DR^{liver}

The resected liver metastases had been subjected to hematoxylin and eosin staining on glass slides, which were reviewed to identify keloid-like collagen and myxoid stroma. Keloid-like collagen was defined as fragmented thick bundles of collagen with brightly eosinophilic hyalinization, which is typically observed in a keloid. Myxoid stroma was defined as an amorphous stromal substance composed of amphiphilic or slightly basophilic extracellular matrix, which is usually intermingled with randomly oriented hyalinized collagen [27].

The histological findings for DR^{liver} were categorized as mature, intermediate, or immature based on the presence of keloid-like collagen and myxoid stroma (Fig. 1) [26]. The slides were initially scanned at low-power magnification to identify myxoid stroma or keloid-like collagen in and around the entire metastatic liver lesion. DR^{liver} was categorized as immature when fibrotic stroma with myxoid changes was observed. The minimum amount of myxoid stroma that can be regarded as immature was the volume that completely filled the microscopic field of a $\times 40$ objective lens. In tumors with no myxoid stroma, DR^{liver} was categorized as intermediate when keloid-like collagen was intermingled with mature stroma, typically with parallel orientation to the mature collagen fibers. DR^{liver} was categorized as mature when the fibrotic stroma did not contain myxoid stroma or keloid-like collagen and was only composed of fine mature collagen fibers stratified into multiple layers.

All available hematoxylin and eosin-stained glass slides were reviewed, and all metastatic lesions were evaluated in cases with multiple liver metastases. The final DR^{liver} categorization in cases with multiple metastases was defined as the least mature DR type among all metastatic lesions. The DR categorization of the primary tumor (DR^{primary}) was evaluated in the reactive fibrous zone at the extramural invasive front, as previously described [32].

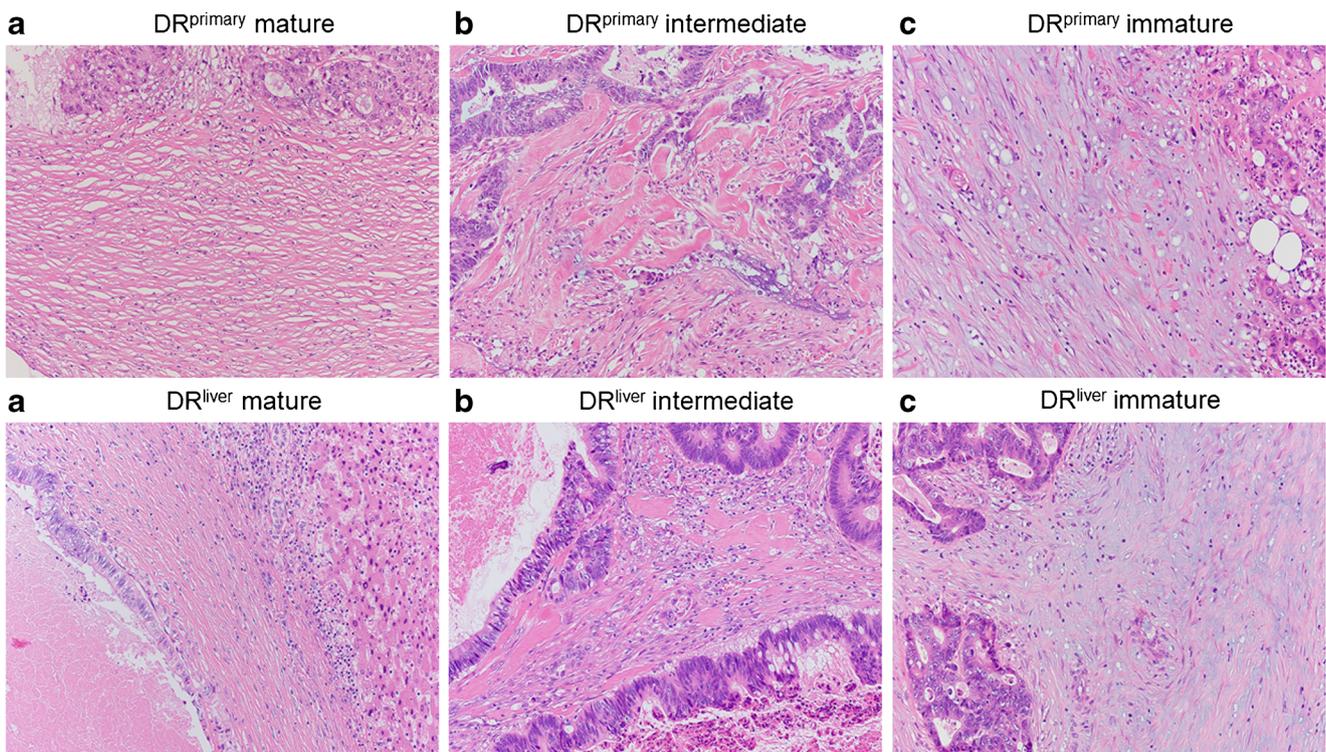


Fig. 1 Categorization of desmoplastic reaction in the primary tumor (DR^{primary}) and in the colorectal liver metastases (DR^{liver}). **a** Mature DR involves fibrotic stroma not accompanied by keloid-like collagen and myxoid stroma, which is typically composed of fine and elongated collagen fibers stratified into multilayers. **b** Intermediate DR is identified based on keloid-like collagen (i.e., fragmented broad bands of collagen

with brightly eosinophilic hyalinization similar to those seen in a keloid). **c** Immature DR is identified based on abundant amorphous extracellular matrix with keloid-like collagen forming the component of myxoid stroma. All images were obtained using a $\times 20$ objective lens and reflect hematoxylin and eosin staining

Statistical analyses

Associations between factors were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Spearman rank correlation coefficients were calculated for DR^{liver} status and DR^{primary} status. Survival curves were compared using the Kaplan-Meier method and the log-rank test. After the histological categorization, each clinical and pathological variable was entered into a Cox proportional hazard regression model to identify factors that independently predicted postoperative survival. Differences were considered statistically significant at P values of < 0.05 . All statistical analyses were performed using JMP® Pro 14 software (SAS Institute, Cary, NC, USA).

Results

Clinicopathological characteristics of each DR^{liver} category

The hepatic lesions were categorized as mature DR^{liver} (12 cases), intermediate DR^{liver} (101 cases), or immature DR^{liver} (91 cases). The associations between the DR^{liver} categories and clinicopathological characteristics are shown in Table 1.

Immature DR^{liver} was significantly associated with a high serum CEA level ($P = 0.032$; Table 1). Among the 160 patients with an evaluable primary tumor, DR^{liver} was correlated with DR^{primary} (Spearman's $\rho = 0.3$, $P = 0.0001$). However, DR^{liver} was not significantly associated with any of the other primary tumor characteristics.

Prognostic value of DR^{liver} categorization

The recurrence rates after hepatectomy were 61.3% for mature/intermediate DR^{liver} and 79.3% for immature DR^{liver} ($P = 0.007$). However, the DR^{liver} categorization was not significantly correlated with the recurrence pattern. The 5-year RFS rates after hepatectomy were 33.8% for mature/intermediate DR^{liver} and 16.7% for immature DR^{liver} ($P = 0.0021$; Fig. 2). The 5-year OS rates after hepatectomy were 64.8% for mature/intermediate DR^{liver} and 35.0% for immature DR^{liver} ($P = 0.0012$; Fig. 2). We also evaluated whether DR^{liver} had prognostic value in the DR^{primary} categories, which revealed that immature DR^{liver} tended to be associated with a poor prognosis for all DR^{primary} categories (Fig. 3). In addition, we examined 126 patients who did not receive preoperative chemotherapy, which revealed that the 5-year RFS rates after hepatectomy were 37.7% for mature/intermediate DR^{liver} and 18.6% for

Table 1 DR^{liver} and clinicopathological characteristics of primary tumor and liver metastasis

Parameters	Categories	No. patients (%) according to DR ^{liver}		P
		Mature/intermediate	Immature	
Liver metastasis				
Timing of metastasis	Synchronous	54 (53.5)	47 (46.5)	0.58
	Metachronous	59 (57.3)	44 (42.7)	
Diameter	< 5 cm	91 (58.0)	66 (42.0)	0.18
	≥ 5 cm	22 (46.8)	25 (53.2)	
Number	1–4	97 (57.7)	71 (42.3)	0.15
	≥ 5	16 (44.4)	20 (55.6)	
Extrahepatic disease	Absence	103 (56.9)	78 (43.1)	0.22
	Presence	10 (43.5)	13 (56.5)	
CEA (ng/mL) ^a	< 5.3	46 (56.7)	24 (34.3)	0.032
	≥ 5.3	65 (50.0)	65 (50.0)	
Preoperative chemotherapy	Absence	72 (57.1)	54 (42.9)	0.52
	Presence	41 (52.6)	37 (47.4)	
Postoperative chemotherapy	Absence	74 (55.6)	59 (44.4)	0.94
	Presence	38 (55.1)	31 (44.9)	
	Unknown	1 (50.0)	1 (50.0)	
Primary tumor				
Location	Right-sided	25 (61.0)	16 (39.0)	0.44
	Left-sided	88 (54.3)	74 (45.7)	
Histological type	tub1	32 (56.1)	25 (43.9)	0.95
	tub2	48 (52.3)	42 (46.7)	
	por/muc/sig	7 (53.8)	6 (46.2)	
T stage	T1/2	5 (50.0)	5 (50.0)	0.34
	T3	64 (58.2)	46 (41.8)	
	T4	18 (45.0)	22 (55.0)	
N stage	N0	42 (61.8)	26 (38.2)	0.16
	N1	28 (45.2)	34 (54.8)	
	N2	17 (56.7)	13 (43.3)	
Lymphatic invasion	Absence	15 (68.2)	7 (31.8)	0.16
	Presence	72 (52.2)	66 (47.8)	
Venous invasion	Absence	3 (37.5)	5 (62.5)	0.53
	Presence	84 (55.3)	68 (44.7)	
DR in the primary tumor	Mature/intermediate	66 (66.0)	34 (34.0)	0.0001
	Immature	21 (35.0)	39 (65.0)	

^a Among 200 patients for whom the preoperative CEA level was known; CEA, carcinoembryonic antigen; DR, desmoplastic reaction

immature DR^{liver} ($P = 0.0074$). The 5-year OS rates after hepatectomy in this group were 61.4% for mature/intermediate DR^{liver} and 37.8% for immature DR^{liver} ($P = 0.065$).

Multivariate analyses of RFS and OS

The post-hepatectomy RFS was significantly predicted by the primary tumor's T and N status, the timing of liver metastasis, and DR^{liver}. The multivariate Cox proportional hazard model revealed that RFS was independently predicted by DR^{liver} and T status (Table 2). The post-hepatectomy OS was significantly

predicted by the number of liver metastases, DR^{liver}, and extrahepatic disease. The multivariate Cox proportional hazard model revealed that OS was independently predicted by DR^{liver}, the number of liver metastases, and extrahepatic metastasis (Table 2).

Discussion

To the best of our knowledge, the present study is the first to reveal that DR^{liver} could independently predict RFS and OS

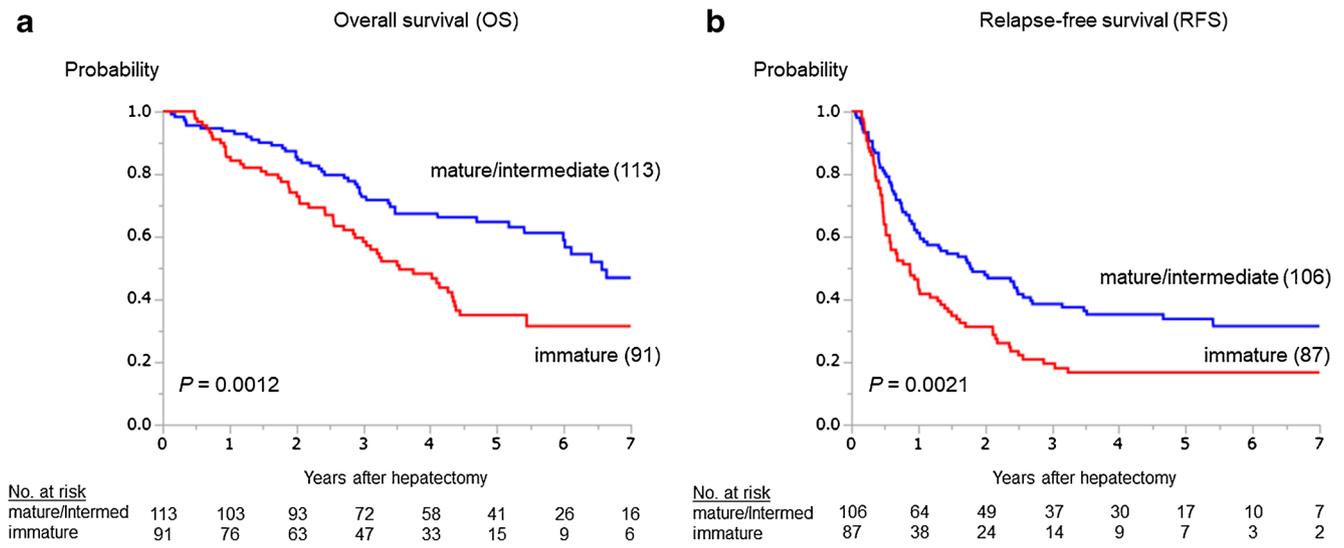


Fig. 2 Survival estimates after hepatectomy for colorectal liver metastases according to desmoplastic reaction categorization in colorectal liver metastases (DR^{liver}). **a** Rates for mature/intermediate DR^{liver} (33.8%) and immature DR^{liver} (16.7%) ($P = 0.0021$). **b** Rates for

mature/intermediate DR^{liver} (64.8%) and immature DR^{liver} (35.0%) ($P = 0.0012$). The numbers within parentheses denote the 5-year survival rate. RFS, relapse-free survival; OS, overall survival

among patients with CRLM. In this context, recent basic research has demonstrated that the tumor microenvironment plays a major role in regulating metastatic ability and determining oncological outcomes [1, 9]. A tumor’s DR is reflected in the formation of excessive fibrous or connective tissue around the tumor, with cancer-associated fibroblasts playing an important role in the formation of DR [8, 13]. These cells also contribute to the microenvironmental regulation of tumor

metastasis, such as tumor angiogenesis, immunosuppression, tumor cell proliferation and aggressiveness, and genetic instability [9, 10, 13, 14, 19, 20].

Various cancers can exhibit DR, including colorectal cancer and pancreatic cancer [2]. It has been also reported that pancreatic cancer patients can be divided into three prognostic groups using our DR categorization criteria [22, 34]. Previous studies have also indicated substantial intra-observer

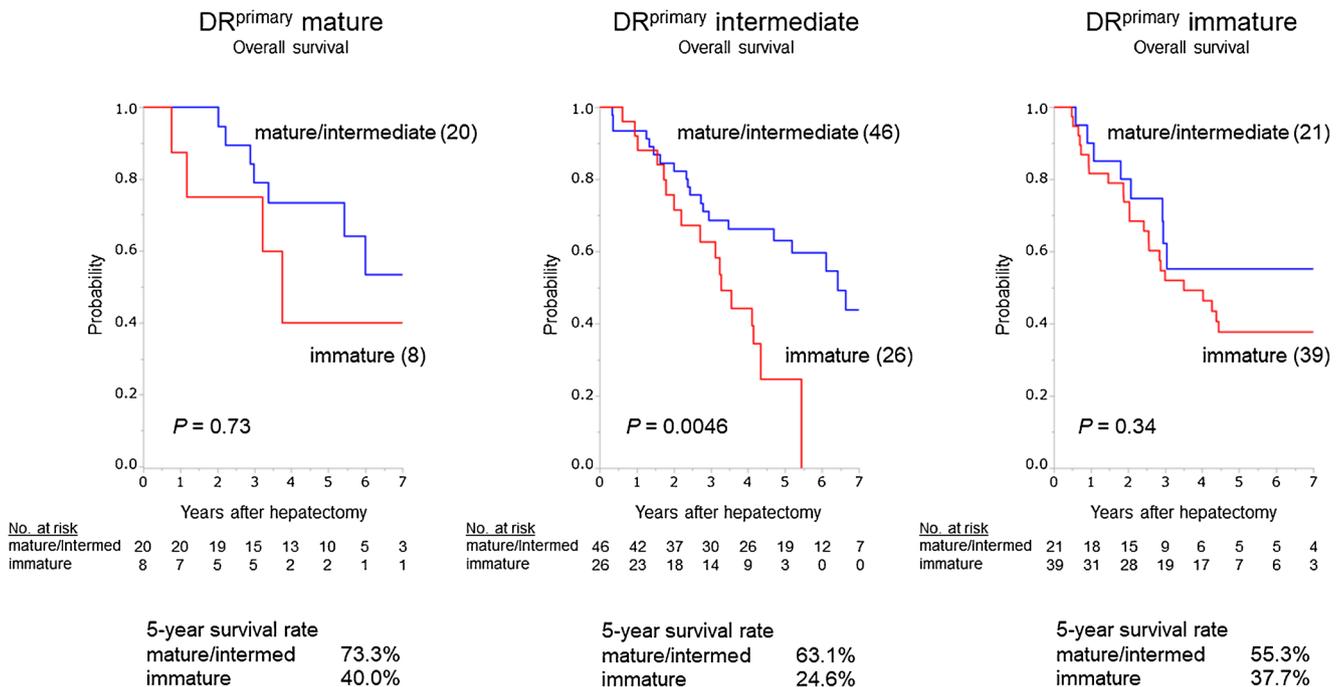


Fig. 3 Survival estimates after hepatectomy for colorectal liver metastases according to desmoplastic reaction in colorectal liver metastases (DR^{liver}) in each primary tumor’s desmoplastic reaction

categorization (DR^{primary}). Immature DR^{liver} cases tended to have a poor prognosis for all DR^{primary} patterns, with an statistically poor prognosis for intermediate DR^{primary} ($P = 0.0046$)

Table 2 Univariate and multivariate analyses for RFS and OS in patients undergoing hepatectomy for CRLM

Parameters	Categories	No.	RFS				OS			
			Univariate		Multivariate		Univariate		Multivariate	
			5-year survival (%)	<i>P</i>	HR (95%CI)	<i>P</i>	5-year survival (%)	<i>P</i>	HR (95%CI)	<i>P</i>
Primary tumor										
T stage	T1/2	10	70.0	0.0026	1	0.013	10	88.9	0.14	–
	T3	103	25.6		3.6 (1.3–14.8)		110	47.3		
	T4	38	9.5		4.6 (1.6–19.5)		40	45.7		
N stage	N0	65	35.2	0.026	NS		68	59.4	0.086	–
	N1	58	15.2				62	45.5		
	N2	28	21.2				30	34.9		
Histological type	tub1	54	36.1	0.071	–		57	57.9	0.49	–
	tub2	84	19.2				90	45.3		
	por/muc /sig	13	15.4				13	42.0		
Lymphatic invasion	Absence	21	33.3	0.84	–		22	52.8	0.67	–
	Presence	130	23.6				138	48.7		
Venous invasion	Absence	7	57.1	0.35	–		8	58.3	0.95	–
	Presence	144	23.6				152	48.9		
Liver metastasis										
Timing of metastasis	Synchronous	82	14.8	0.0006	NS		88	44.9	0.39	–
	Metachronous	69	37.3				72	55.2		
Tumor diameter (mm)	< 50	117	28.2	0.25	–		126	51.1	0.33	–
	≥ 50	34	14.7				34	44.5		
Number	< 5	125	27.0	0.10			132	54.5	0.0019	1
	≥ 5	26	15.4				28	26.5		2.1 (1.3–3.4)
DR ^{liver}	Mature/intermediate	81	32.5	0.0069	1	0.021	87	63.7	0.0054	1
	Immature	70	16.0		1.6 (1.1–2.2)		73	33.6		1.8 (1.2–2.9)
Extrahepatic disease	Absence	138	53.7	0.15	–		139	53.7	0.0018	1
	Presence	13	15.4				21	23.8		2.5 (1.4–4.2)
CEA (ng/mL)	< 5.3	53	27.0	0.27	–		60	57.1	0.092	–
	≥ 5.3	92	24.1				97	45.8		

NS, not selected; RFS, relapse-free survival; OS, overall survival; CRLM, colorectal liver metastasis; DR, desmoplastic reaction

agreement ($\kappa = 0.79$) and inter-observer agreement ($\kappa = 0.69$) regarding DR categorization [30, 31].

Our previous research has indicated that intermediate stroma is immunohistochemically characterized by the excessive deposition of collagen 1 [27], which promotes cancer proliferation and treatment resistance. [5] In addition, immature stroma is characterized by hypovascularity and a restricted distribution of immune cells, with abundant tumor-supporting extracellular components (e.g., fibronectin and tenascin) and intact expression of mismatch repair gene protein [26, 27, 31, 36]. Thus, the DR categorization system appears to reflect metastasis-associated molecular events in the cancer microenvironment, which may be useful for predicting prognosis among patients with CRC.

Duda et al. have demonstrated that metastatic cancer cells can transport their stromal components, including activated fibroblasts, from the primary tumor site [6]. The present study also evaluated the primary and metastatic sites' DR categorization, which revealed that DR^{liver} was positively correlated with DR^{primary}. This finding implies that the DR categorization of the metastatic site frequently parallels that of the primary tumor, although we noted disagreement between the DR^{liver} and DR^{primary} for some patients. Takahashi et al. have investigated metastatic lymph nodes (MLNs) and reported that there was histopathological heterogeneity between the primary tumors and their synchronous MLNs [23]. Furthermore, Mori et al. have demonstrated that accurate prognostication could be achieved by combining the histological types of the primary tumors and their synchronous MLNs [17]. We also observed that immature

DR^{liver} was associated with a poor prognosis for each DR^{primary} category, especially for the intermediate DR^{primary} category. This relationship may be explained by the fact that many patients underwent hepatectomy at varying intervals after the primary resection, which suggests that the DR^{liver} status may reflect the most recent malignant potential and provide better prognostic value relative to the DR^{primary} status.

Preoperative chemotherapy might have a significant effect on tumor histology, including stromal status. Thus, we also evaluated patients who did not receive preoperative chemotherapy and confirmed a similar trend in the relationship between DR^{liver} status and prognosis. However, there was only a marginally significant difference in the OS rates (the numerical results are noticeably different [61.4% vs. 37.8%], and while the *P* value does not meet the cut-off for significance, it is fairly close [*P* = 0.065]). The absence of a significant difference may be related to the small number of patients without preoperative chemotherapy, which would have limited the power of the analyses. In addition, the group of patients without preoperative chemotherapy included many cases with a small number of liver metastases, which also had relatively small diameters. Thus, these patients would be expected to have a good prognosis and experience few events, which might help explain the absence of a significant difference. A recent study also revealed that the effects of anti-VEGF therapy depend on the status of the invasive front in CRLM [7]. In the present study, 20 patients received preoperative chemotherapy that included anti-VEGF antibodies, although the use of anti-VEGF antibodies was not significantly related to the distribution of the DR^{liver} patterns (data not shown).

We acknowledge that the present study has several limitations. First, the study sample was relatively small and was treated at a single center. Second, the study's design was retrospective, with patients receiving various treatments before or after the hepatectomy, including adjuvant chemotherapy. Thus, additional multi-center studies are needed to determine whether DR^{liver} categorization can be used in clinical practice, and whether this factor can predict the therapeutic effect of postoperative adjuvant chemotherapy.

In conclusion, the present study revealed that the DR categorization could be evaluated for CRLM, similar to its evaluation for the primary tumor. In addition, the DR^{liver} status was positively correlated with the DR^{primary} status, which implies that stromal components accompany cancer cells to distant metastatic sites. Thus, both cancer cells and the stroma should be considered therapeutic targets in cancer treatment strategies. Furthermore, immature DR^{liver} was associated with a poor prognosis after hepatectomy. Therefore, evaluating DR^{liver} could provide more precise information regarding tumor aggressiveness at the metastatic site.

Contribution statement Tadakazu Ao and Yoshiki Kajiwara conceived and designed the study, and wrote, edited, and reviewed the manuscript.

Keisuke Yonemura and Sufumi Aosasa collected the data and reviewed the manuscript. Eiji Shinto, Satsuki Mochizuki, and Koichi Okamoto revised the manuscript. Hideki Ueno conceived and designed the study, and reviewed manuscript. All authors approved the final version of the manuscript for publication. Tadakazu Ao takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

Ethical responsibilities of authors section The experiments reported here were carried out in agreement with the Declaration of Helsinki and were approved by the Ethics Committee of the National Defense Medical College Hospital (Tokorozawa, Japan).

Conflicts of interest The authors declare that they have no conflict of interest.

References

- Allen M, Louise Jones J (2011) Jekyll and Hyde: the role of the microenvironment on the progression of cancer. *J Pathol* 223:162–176. <https://doi.org/10.1002/path.2803>
- Apte MV, Park S, Phillips PA, Santucci N, Goldstein D, Kumar RK, Ramm GA, Buchler M, Friess H, McCarrroll JA, Keogh G, Merrett N, Pirola R, Wilson JS (2004) Desmoplastic reaction in pancreatic cancer: role of pancreatic stellate cells. *Pancreas* 29:179–187
- Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, Nitta H, Yoshidome H, Hatano E, Ueno M, Takamura H, Baba H, Kosuge T, Kokudo N, Takahashi K, Endo I, Wakabayashi G, Miyazaki M, Uemoto S, Ohta T, Kikuchi K, Yamaue H, Yamamoto M, Takada T (2012) 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* 19:72–84. <https://doi.org/10.1007/s00534-011-0460-z>
- Bonney GK, Coldham C, Adam R, Kaiser G, Barroso E, Capussotti L, Laurent C, Verhoef C, Nuzzo G, Elias D, Lapointe R, Hubert C, Lopez-Ben S, Krawczyk M, Mirza DF (2015) Role of neoadjuvant chemotherapy in resectable synchronous colorectal liver metastasis; an international multi-center data analysis using LiverMetSurvey. *J Surg Oncol* 111:716–724. <https://doi.org/10.1002/jso.23899>
- Conti JA, Kendall TJ, Bateman A, Armstrong TA, Papa-Adams A, Xu Q, Packham G, Primrose JN, Benyon RC, Iredale JP (2008) The desmoplastic reaction surrounding hepatic colorectal adenocarcinoma metastases aids tumor growth and survival via alpha v integrin ligation. *Clin Cancer Res* 14:6405–6413. <https://doi.org/10.1158/1078-0432.Ccr-08-0816>
- Duda DG, Duyverman AM, Kohno M, Snuderl M, Steller EJ, Fukumura D, Jain RK (2010) Malignant cells facilitate lung metastasis by bringing their own soil. *Proc Natl Acad Sci U S A* 107:21677–21682. <https://doi.org/10.1073/pnas.1016234107>
- Frentzas S, Simoneau E, Bridgeman VL, Vermeulen PB, Foo S, Kostaras E, Nathan M, Wotherspoon A, Gao ZH, Shi Y, Van den Eynden G, Daley F, Peckitt C, Tan X, Salman A, Lazaris A, Gazinska P, Berg TJ, Eltahir Z, Ritsma L, Van Rheeën J, Khashper A, Brown G, Nystrom H, Sund M, Van Laere S, Loyer E, Dirix L, Cunningham D, Metrakos P, Reynolds AR (2016) Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med* 22:1294–1302. <https://doi.org/10.1038/nm.4197>

8. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144:646–674. <https://doi.org/10.1016/j.cell.2011.02.013>
9. Joyce JA, Pollard JW (2009) Microenvironmental regulation of metastasis. *Nat Rev Cancer* 9:239–252. <https://doi.org/10.1038/nrc2618>
10. Kalluri R, Zeisberg M (2006) Fibroblasts in cancer. *Nat Rev Cancer* 6:392–401. <https://doi.org/10.1038/nrc1877>
11. Koike M, Yasui K, Torii A, Kodama S (2000) Prognostic significance of entrapped liver cells in hepatic metastases from colorectal cancer. *Ann Surg* 232:653–657
12. Lee WS, Kim MJ, Yun SH, Chun HK, Lee WY, Kim SJ, Choi SH, Heo JS, Joh JW, Kim YI (2008) Risk factor stratification after simultaneous liver and colorectal resection for synchronous colorectal metastasis. *Langenbeck's Arch Surg* 393:13–19. <https://doi.org/10.1007/s00423-007-0231-0>
13. McAllister SS, Weinberg RA (2010) Tumor-host interactions: a far-reaching relationship. *J Clin Oncol* 28:4022–4028. <https://doi.org/10.1200/JCO.2010.28.4257>
14. McDonald LT, LaRue AC (2012) Hematopoietic stem cell derived carcinoma-associated fibroblasts: a novel origin. *Int J Clin Exp Pathol* 5:863–873
15. Merkel S, Bialecki D, Meyer T, Muller V, Papadopoulos T, Hohenberger W (2009) Comparison of clinical risk scores predicting prognosis after resection of colorectal liver metastases. *J Surg Oncol* 100:349–357. <https://doi.org/10.1002/jso.21346>
16. Minagawa M, Yamamoto J, Kosuge T, Matsuyama Y, Miyagawa S, Makuuchi M (2007) Simplified staging system for predicting the prognosis of patients with resectable liver metastasis: development and validation. *Arch Surg (Chicago, Ill: 1960)* 142:269–276; discussion 277. <https://doi.org/10.1001/archsurg.142.3.269>
17. Mori T, Hirota T, Ohashi Y, Kodaira S (2006) Significance of histologic type of primary lesion and metastatic lymph nodes as a prognostic factor in stage III colon cancer. *Dis Colon Rectum* 49:982–992. <https://doi.org/10.1007/s10350-006-0531-4>
18. Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. *World J Surg* 22:268–276 discussion 276–267
19. Ostman A, Augsten M (2009) Cancer-associated fibroblasts and tumor growth—bystanders turning into key players. *Curr Opin Genet Dev* 19:67–73. <https://doi.org/10.1016/j.gde.2009.01.003>
20. Pietras K, Ostman A (2010) Hallmarks of cancer: interactions with the tumor stroma. *Exp Cell Res* 316:1324–1331. <https://doi.org/10.1016/j.yexcr.2010.02.045>
21. Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S (2005) Analysis of preoperative prognostic factors for long-term survival after hepatic resection of liver metastasis of colorectal carcinoma. *J Gastrointest Surg* 9:374–380. <https://doi.org/10.1016/j.gassur.2004.09.031>
22. Sinn M, Denkert C, Striefler JK, Pelzer U, Stieler JM, Bahra M, Lohneis P, Dorken B, Oettle H, Riess H, Sinn BV (2014) Alpha-smooth muscle actin expression and desmoplastic stromal reaction in pancreatic cancer: results from the CONKO-001 study. *Br J Cancer* 111:1917–1923. <https://doi.org/10.1038/bjc.2014.495>
23. Takahashi K, Mori T, Yasuno M (2000) Histologic grade of metastatic lymph node and prognosis of rectal cancer. *Dis Colon Rectum* 43:S40–S46
24. Tan MC, Castaldo ET, Gao F, Chari RS, Linehan DC, Wright JK, Hawkins WG, Siegel BA, Delbeke D, Pinson CW, Strasberg SM (2008) A prognostic system applicable to patients with resectable liver metastasis from colorectal carcinoma staged by positron emission tomography with [¹⁸F]fluoro-2-deoxy-D-glucose: role of primary tumor variables. *J Am Coll Surg* 206:857–868; discussion 868–859. <https://doi.org/10.1016/j.jamcollsurg.2007.12.023>
25. Tanaka K, Shimada H, Ueda M, Matsuo K, Endo I, Togo S (2007) Long-term characteristics of 5-year survivors after liver resection for colorectal metastases. *Ann Surg Oncol* 14:1336–1346. <https://doi.org/10.1245/s10434-006-9071-3>
26. Ueno H (2004) Histological categorisation of fibrotic cancer stroma in advanced rectal cancer. *Gut* 53:581–586. <https://doi.org/10.1136/gut.2003.028365>
27. Ueno H, Jones A, Jass JR, Talbot IC (2002) Clinicopathological significance of the ‘keloid-like’ collagen and myxoid stroma in advanced rectal cancer. *Histopathology* 40:327–334
28. Ueno H, Hase K, Hashiguchi Y, Shimazaki H, Tanaka M, Miyake O, Masaki T, Shimada Y, Kinugasa Y, Mori Y, Kishimoto M, Kameoka S, Sato Y, Matsuda K, Nakadoi K, Shinto E, Nakamura T, Sugihara K (2014) Site-specific tumor grading system in colorectal cancer: multicenter pathological review of the value of quantifying poorly differentiated clusters. *Am J Surg Pathol* 38:197–204. <https://doi.org/10.1097/pas.0000000000001113>
29. Ueno H, Shinto E, Kajiwara Y, Fukazawa S, Shimazaki H, Yamamoto J, Hase K (2014) Prognostic impact of histological categorisation of epithelial-mesenchymal transition in colorectal cancer. *Br J Cancer* 111:2082–2090. <https://doi.org/10.1038/bjc.2014.509>
30. Ueno H, Shinto E, Hashiguchi Y, Shimazaki H, Kajiwara Y, Sueyama T, Yamamoto J, Hase K (2015) In rectal cancer, the type of desmoplastic response after preoperative chemoradiotherapy is associated with prognosis. *Virchows Arch* 466:655–663. <https://doi.org/10.1007/s00428-015-1756-1>
31. Ueno H, Shinto E, Shimazaki H, Kajiwara Y, Sueyama T, Yamamoto J, Hase K (2015) Histologic categorization of desmoplastic reaction: its relevance to the colorectal cancer microenvironment and prognosis. *Ann Surg Oncol* 22:1504–1512. <https://doi.org/10.1245/s10434-014-4149-9>
32. Ueno H, Sekine S, Oshiro T, Kanemitsu Y, Hamaguchi T, Shida D, Takashima A, Ishiguro M, Ito E, Hashiguchi Y, Kondo F, Shimazaki H, Mochizuki S, Kajiwara Y, Shinto E, Yamamoto J, Shimada Y (2017) Disentangling the prognostic heterogeneity of stage III colorectal cancer through histologic stromal categorization. *Surgery*. <https://doi.org/10.1016/j.surg.2017.09.007>
33. Van den Eynden GG, Bird NC, Majeed AW, Van Laere S, Dirix LY, Vermeulen PB (2012) The histological growth pattern of colorectal cancer liver metastases has prognostic value. *Clin Exp Metastasis* 29:541–549. <https://doi.org/10.1007/s10585-012-9469-1>
34. Wang LM, Silva MA, D'Costa Z, Bockelmann R, Soonawalla Z, Liu S, O'Neill E, Mukherjee S, McKenna WG, Muschel R, Fokas E (2016) The prognostic role of desmoplastic stroma in pancreatic ductal adenocarcinoma. *Oncotarget* 7:4183–4194. <https://doi.org/10.18632/oncotarget.6770>
35. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD 3rd, Dorfman GS, Eng C, Fong Y, Giusti AF, Lu D, Marsland TA, Michelson R, Poston GJ, Schrag D, Seidenfeld J, Benson AB 3rd (2010) American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 28:493–508. <https://doi.org/10.1200/jco.2009.23.4450>
36. Wright CL, Stewart ID (2003) Histopathology and mismatch repair status of 458 consecutive colorectal carcinomas. *Am J Surg Pathol* 27:1393–1406
37. Zlobec I, Lugli A (2009) Invasive front of colorectal cancer: dynamic interface of pro-/anti-tumor factors. *World J Gastroenterol* 15:5898–5906

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.