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Prognostic Impact of N2 of the Primary Tumour in Surgical Resection for Colorectal Liver Metastases

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Abstract. *Background/Aim: The status of lymph node metastasis of primary tumours remains to be completely investigated. This study investigated the prognostic impact of the degree of primary lymph node metastasis in patients with colorectal liver metastasis. Patients and Methods: We retrospectively analysed the clinical data of 106 patients with colorectal liver metastases who underwent surgical resection. Prognostic factors, including the degree of the positive primary lymph nodes, positive lymph node ratio, and log odds of positive lymph nodes, were evaluated. Results: The T factor and N2 status were independent risk factors for overall survival in patients who underwent surgical resection. Survival was significantly lower in the N2 group than in the N0-1 group. Additionally, ≥N2 status showed better prognostic performance than ≥N1 status. Conclusion: N2 of primary tumours is an independent useful prognostic factor in colorectal liver metastasis and can help determine the indication of surgical resection and pre/post-operative chemotherapy.*

Previously, synchronous metastases, primary lymph node metastasis, number of tumours, extrahepatic metastasis at hepatectomy, and preoperative tumour marker levels were reported as prognostic factors for colorectal liver metastasis (1). Of these factors, the status of lymph node metastasis of the primary tumour remains to be completely investigated in terms of its prognostic impact. For example, the clinical risk score reported by Fong *et al*. is a well-known risk index for surgical resection of colorectal liver metastasis (2). According to this risk score, the lymph node of the primary tumour was evaluated as positive or negative only. Other prognostic indices or risk indices also evaluated the lymph node of the primary tumour in the same manner (3). However, the correlation between the degree of primary lymph node metastasis and the prognosis of patients with liver metastasis has not been well investigated.

Therefore, this study investigated the detailed prognostic value of lymph node metastasis in primary colorectal tumours to strengthen the accuracy of prognosis prediction, enhance our understanding of the indications for pre- and postoperative treatment, and potentially improve the outcomes of patients with colorectal liver metastasis.

Patients and Methods

Subjects. Clinical data of 111 patients with colorectal liver metastasis who underwent surgical resection at the Tokyo Medical University Hachioji Medical Center between June 2007 and July 2020 were retrospectively analysed. Patients with extrahepatic metastasis to the lung, lymph nodes, and peritoneal dissemination (N=5) were excluded, leaving 106 patients included in the study. All patients underwent surgical resection for the primary tumour before or at the same time as surgery for liver metastasis. This helped prevent stenosis or bleeding due to the primary tumour.

Pathological definition of the primary tumour. The primary tumour was pathologically diagnosed based on the TNM classification system of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) guidelines. The classification of lymph node metastasis in colorectal cancer was also determined based on these guidelines. All regional lymph nodes were dissected, regardless of the degree of tumour progression. The dissected lymph nodes were removed from the tumour specimen and classified according to the guidelines.

The lymph nodes of the primary tumour were also evaluated using positive lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS). These were calculated as follows:

LNR=positive lymph node/dissected lymph node,

LODDS=log [(positive lymph node + 0.5)/(negative lymph node + 0.5)].

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The LNR was classified according to a system proposed by Berger *et al*. (4) and Rosenberg *et al*. (5), as follows: Berger *et al*., LNR1<0.05, 0.05≤LNR2<0.19, 0.19≤LNR3<0.39, and 0.39≤LNR4≤1.00; Rosenberg *et al*., LNR0=0.00, 0.01≤LNR1≤0.17, 0.18≤LNR2≤0.41, 0.42≤LNR3≤0.69, and LNR4≥0.70. The LODDS was classified according to the classification proposed by Wang *et al*. (6) and Persiani *et al*. (7) as follows: Wang *et al*., LODDS1<–2.2, –2.2≤LODDS2<–1.1, –1.1≤LODDS3<0.0, 0.0≤LODDS4<1.1, and LODDS5≥1.1; Persiani *et al*., LODDS1 ≤–1.36, –1.36<LODDS2≤-0.53, and LODDS3 >–0.53.

Treatment strategy for liver metastasis. Surgical resection, with or without preoperative treatment, was performed primarily when the liver metastasis could be resected technically and oncologically. Preoperative treatment was performed in cases wherein the risk of recurrence was high, such as cases of multiple synchronous metastases or difficult resection based on technical or oncological aspects. The surgical procedure used was selected based on anatomical tumour factors. Percutaneous transhepatic portal vein embolization was performed preoperatively when required.

Comparison of overall survival between ≥N1 and ≥N2. Overall survival was compared between the ≥N1 and ≥N2 statuses of the TNM classification of the primary tumour; it was defined as the duration of survival from the beginning of treatment for liver metastasis to the last follow-up or death by any cause. The prognostic factors for overall survival were evaluated using univariate and multivariate analyses. Moreover, prognosis was compared among N0, N1, and N2 of the TNM classification of the primary tumour. Additionally, the prognostic performance of ≥N1 and ≥N2 for 1-, 3-, 5-, and 7-year survival groups was compared.

Statistical analyses. Continuous variables are expressed as median with range (minimum–maximum), and the Mann–Whitney *U*-test was used for between-group comparisons. Categorical variables are expressed as number (%) and compared using the chi-square test or Fisher's exact test, as required. Univariate and multivariate analyses were performed using Cox proportional hazards regression analysis with forward selection of the likelihood ratio. The prognosis was evaluated using the Kaplan–Meier method, and statistical differences were evaluated using the log-rank test. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical statements. The procedures followed were in accordance with the ethical standards of the institutional review board of the Tokyo Medical University (T2019-0149). Informed consent was obtained from all individual participants included in the study.

Results

Patient characteristics, including a comparison between N0-1 and N2 of the primary tumour, are shown in Table I. The number of dissected lymph nodes was significantly higher in the N2 group than in the N0-1 group (p=0.001). However, even in the N0-1 group, five or more lymph nodes were dissected in 69 (94.5%) patients and 10 or more lymph nodes were dissected in 47 (64.4%) patients.

In the univariate analysis, the T factor of the TNM classification, ≥N2 status, LNR classification by Berger *et al*. and Rosenberg *et al*., LODDS classification by Wang *et al*. and Persiani *et al*., and preoperative levels of carcinoembryonic antigen (CEA) significantly differed (Table II). Multivariate analysis showed that the T factor and N2 status of the TNM classification were independent risk factors of overall survival after surgical resection for colorectal liver metastasis. When comparing prognoses associated with N0, N1, and N2 statuses of a primary tumour, the survival outcome of the N2 group was poorer than that of the other two groups (Figure 1). Comparing prognostic performance between ≥N1 and ≥N2 of the primary tumour, ≥N2 showed a better outcome than ≥N1 in all groups for 1- to 7-year survival (Table III). The positive predictive value, negative predictive value, and odds ratio were higher in ≥N2 than in ≥N1 in all 1- to 7-year survival groups. In addition, significant differences were found between ≥N2 and ≥N1 regarding 3-, 5-, and 7-year survival.

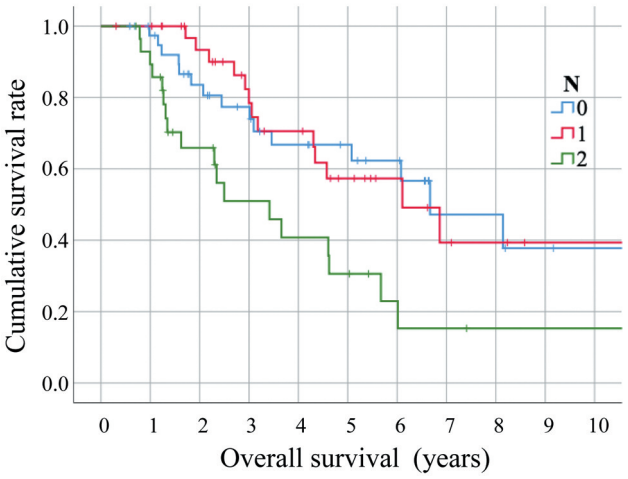

Figure 1. *Comparison of prognosis among N0, N1, and N2 of the TNM classification of primary tumour. Statistical differences between each pair were as follows: N0-N1, p=0.908; N1-N2, p=0.007; and N0-N2, p=0.008.*

Discussion

According to a previous report, the prognosis of patients with stage III colorectal cancer varied with the number of positive lymph nodes (8), which led to the differences between IIIA and IIIC stages in the AJCC/UICC classification. Thus, as the prognosis of advanced colorectal cancer without metastasis differs with the number of positive lymph nodes, the prognosis in patients with colorectal liver metastasis (stage IV) might also be affected by the number of positive lymph nodes of the primary tumour.

Several methods have been considered for evaluating lymph nodes, such as the number of positive lymph nodes, LNR, metastatic lymph node size, and tumour differentiation

Table I. *Patient characteristics*.

			All cases N=106	N0-1 of primary tumour N=77	N2 of primary tumour N=29	*p*-Value
General background						
Age						
Resection of liver metastasis		Years	68 (19-85)	68 (37-82)	68 (19-85)	0.718
Gender						
Male/female			65/41	49/28	16/13	0.425
Primary tumour information						
Tumour location						
Cecum		%	7 (6.6)	5 (6.5)	2 (6.9)	0.996
Ascending colon			14 (13.2)	10 (13.0)	4 (13.8)	
Transverse colon			9 (8.5)	6 (7.8)	3 (10.3)	
Descending colon			5 (4.7)	4 (5.2)	1 (3.4)	
Sigmoid colon			28 (26.4)	21 (27.3)	7 (24.1)	
Rectum			43 (40.6)	31 (40.3)	12 (41.4)	
Differentiation						
G1/G2/G3		n	40/63/0	30/44/0	10/19/0	0.570
T						
1/2/3/4			1/11/73/21	1/8/55/13	0/3/18/8	0.622
Number of positive lymph nodes			1 (0-46)	0 (0-3)	7 (4-46)	<0.001
Number of dissected lymph nodes			19 (2-86)	14 (2-85)	25 (8-86)	0.001
Positive lymph node ratio (LNR)		%	6.8 (0.0-84.6)	0.0 (0.0-42.9)	26.7 (6.9-84.6)	<0.001
Classification by Berger *et al*.	1/2/3/4		47/27/14/14	47/18/3/5	0/9/11/9	<0.001
Classification by Rosenberg *et al*.	0/1/2/3/4		38/35/18/7/4	38/26/7/2/0	0/9/11/5/4	<0.001
Log odds of positive lymph nodes (LODDS)			–0.95 (–2.23-0.66)	–0.42 (–1.08-0.66)	–1.22 (–2.23- –0.11)	<0.001
Classification by Wang *et al*.	1/2/3/4		1/44/49/8	1/44/28/0	0/0/21/8	<0.001
Classification by Persiani *et al*.	1/2/3		25/51/26	25/40/8	0/11/18	<0.001
RAS mutation		%	37 (36.6)	25 (34.7)	12 (41.4)	0.530
Liver metastasis information						
Synchronous/metachronous		n	52/54	34/43	18/11	0.100
Number of tumours			2 (1-15)	2 (1-15)	2 (1-8)	0.583
Maximum tumour size		cm	3.0 (1.0-11.0)	3.0 (1.0-11.0)	3.0 (1.0-8.0)	0.234
Surgical information of liver metastasis						
Preoperative treatment						
None		%	44 (41.5)	34 (44.2)	10 (34.5)	0.368
Chemotherapy	FOLFOX base		46 (71.9)	32 (72.7)	14 (70.0)	0.819
	FOLFIRI base		13 (20.3)	8 (18.2)	5 (25.0)	
	Other		5 (7.8)	4 (9.1)	1 (5.0)	
Preoperative tumour markers						
CEA		ng/ml	6.85	6.35	8.35	0.460
CA19-9		U/ml	15.8	18.15	13.795	0.983
Surgical procedure						
Partial or segmentectomy		%	62 (58.5)	46 (59.7)	16 (55.2)	0.499
Sectionectomy			17 (16.0)	10 (13.0)	7 (24.1)	
Hemihepatectomy			24 (22.6)	18 (23.4)	6 (20.7)	
Trisectionectomy			3 (2.8)	3 (3.9)	0 (0.0)	
Resection margin						
R0/R1			104/2	76/1	28/1	0.474
Adjuvant therapy						
None			49 (46.2)	41 (53.2)	16 (55.2)	0.859
Chemotherapy	FOLFOX		24 (42.1)	17 (41.5)	7 (43.8)	0.926
	UFT base		20 (35.1)	15 (36.6)	5 (31.3)	
	Other		13 (22.8)	9 (22.0)	4 (25.0)	
Prognosis						
Median overall survival*		Months	69.0	81.1	41.5	0.001
5-year survival rate*		%	48.6	57.7	27.3	0.017
Median recurrence-free survival**		Months	15.1	18.1	71.7	0.002

Continuous variables are expressed as median (minimum–maximum). Categorical variables are expressed as number of patients (%). CA19-9, Carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; UFT, tegafur and uracil; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; n, number. *From the beginning of treatment for liver metastasis. **From the surgery of liver metastasis.

Table II. *Univariate and multivariate analyses of clinicopathological factors for overall survival.*

		Univariate analysis			Multivariate analysis		
		p-Value	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI
General background							
Age	Resection of liver metastasis	0.586					
Primary tumour information							
Tumour location	Right sided/left sided	0.391					
Differentiation	G1/G2	0.866					
T	1/2/3/4	0.021	1.95	1.11-3.45	0.009	2.15	1.21-3.84
Lymph node classification	≥N1	0.189					
	≥N2	0.002	2.57	1.42-4.68	0.003	2.58	1.38-4.79
Positive lymph node ratio	Classification by Berger *et al.*	0.008	1.41	1.09-1.83	0.815		
	Classification by Rosenberg *et al.*	0.013	1.35	1.07-1.72	0.676		
Log odds of positive lymph nodes	Classification by Wang *et al.*	0.026	1.65	1.06-2.56	0.774		
	Classification by Persiani *et al.*	0.043	1.55	1.01-2.36	0.933		
RAS mutation		0.086			0.111		
Liver metastasis information							
	Synchronous/metachronous	0.336					
Number of tumours		0.771					
Maximum tumour size		0.414					
Surgical information of liver metastasis							
Preoperative treatment		0.906					
Preoperative tumour markers	CEA	0.037	NC	NC	0.080		
	CA19-9	0.144					
Resection margin	R0/R1	0.050			0.374		
Adjuvant therapy		0.986					

CA19-9, Carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; NC, not countable.

Table III. *Comparison of prognostic performance between ≥N1 and ≥N2 of the primary tumour.*

		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds ratio	95% CI	*p*-Value
1-year survival	≥N1	75.0	38.8	4.8	97.4	1.90	0.19-18.94	1.000
	≥N2	75.0	74.5	10.7	98.6	8.76	0.87-88.10	0.062
3-year survival	≥N1	69.2	42.1	35.3	75.0	1.64	0.61-4.38	0.325
	≥N2	46.2	82.5	54.5	77.0	4.03	1.44-11.28	0.006
5-year survival	≥N1	71.1	44.4	57.4	59.3	1.96	0.75-5.13	0.166
	≥N2	42.1	83.3	72.7	57.7	3.64	1.23-10.79	0.017
7-year survival	≥N1	68.9	55.0	77.5	44.0	2.71	0.92-8.00	0.068
	≥N2	40.0	90.0	90.0	40.0	6.00	1.24-29.07	0.016

CI, Confidence interval; NPV, negative predictive value; PPV, positive predictive value.

of metastatic lymph nodes. A previous study found that of these indexes, the LNR classification by Rosenberg *et al.* showed better predictive power than the others, especially when the number of dissected lymph nodes was inadequate. Moreover, they suggested that LODDS showed the best performance and remained unaffected by the number of dissected lymph nodes when analysed as a continuous variable. However, these analyses were concerned with the prognosis of the primary tumour, whereas in the present study, only N2 of the TNM classification between lymph node evaluations was found as an independent risk factor for prognosis of liver metastasis.

Herein, the appropriate cut-off value for the number of positive lymph nodes was between N1 and N2. Wang *et al*. also reported that a lower number of positive lymph nodes is associated with improved survival in patients with colorectal liver metastasis and that the hazard ratio differs between ≤3 and ≥4 of the number of positive lymph nodes (9). Thus, N2 is an effective prognostic marker in colorectal liver metastasis.

Limitations. This study has several limitations. First, it was performed at a single center and included a relatively small number of patients. Second, the disease and treatment course for colorectal liver metastasis was variable. For instance, patients had synchronous versus metachronous tumours, did and did not undergo preoperative treatment, and were treated with and without adjuvant chemotherapy. Therefore, further studies with a larger patient cohort and more uniform disease and treatment characteristics should be performed.

Conclusion

N2 of the primary tumour in the TNM classification is an independent and useful prognostic factor in surgical resection for colorectal liver metastasis. This index will improve outcomes in patients with colorectal liver metastasis.

Conflicts of Interest

The Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Authors' Contributions

KT was involved in project development, data collection and analysis, and original manuscript writing. NC, SO, TG, TK, TS, and EH participated in data collection, critical revision, and final approval of the manuscript. SK was involved in supervision, data collection, critical revision, and final approval of the manuscript.

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