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Role of Node Dissection for Lymphatic Remetastasis in Repeat Hepatectomy for Colorectal Liver Metastasis

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Key Words

Colorectal carcinoma · Liver metastasis · Lymph node metastasis · Hepatectomy

Abstract**Background:** Although the prognosis after hepatectomy for colorectal liver metastasis with hilar node remetastasis is poor, the role of node dissection for lymphatic remetastasis at repeat hepatectomy for hepatic recurrence is unknown.**Methods:** Fifty patients who underwent node dissection plus hepatectomy were retrospectively reviewed and divided into three groups: group I, 38 patients with a negative node; group II, 6 with a positive node at initial hepatectomy, and group III, 6 with a positive node at repeat hepatectomy.**Results:** The 5-year survival rate after initial hepatectomy in group I was 46%. All patients in group II died within 2 years after surgery. In group III, the median survival time was 42 months after repeat hepatectomy, and 4 patients survived for more than 5 years after initial hepatectomy. Disease-free time was more than 1 year after initial hepatectomy in all long-term survivors. In addition, node metastasis was limited around the hepatic pedicle and postpancreatic area in 3 of 4 long-term survivors. **Conclusions:** Node dissection for lymphatic remetastasis may contribute to longer survival only when node metastasis is limited around the hepatic pedicle and postpancreatic area at repeat hepatectomy performed more than 1 year after the initial hepatectomy.

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Introduction

Hepatectomy is the best treatment with a low mortality rate for colorectal liver metastasis [1–3]. The prognosis of patients with hilar node metastasis has been believed to be poor [4, 5], since they are regarded as having extrahepatic metastasis. A current report by Laurent et al. [6] indicated that microscopic hepatic node metastasis was found in 23 out of 156 patients who underwent hepatectomies with systematic hepatic lymph node dissection for colorectal liver metastasis in their prospective study. The prognosis of patients with hepatic hilar node metastasis was poorer than for those without even if systematic lymph node dissection had been performed [6]. Therefore, it is generally accepted that dissection for ‘lymphatic remetastasis’ from colorectal liver metastasis should be carried out under special circumstances.

The recurrence rate for the remnant liver after initial hepatectomy for colorectal liver metastasis is high, and repeat hepatectomy contributes to the improvement of prognosis [7]. Although hilar node metastasis is occasionally found in patients with recurrence in the remnant liver, little information is available on the indications for such lymph node dissection. In this study, we report the outcomes of positive node dissection for patients with hilar node metastasis during repeat hepatectomy and discuss its clinical significance.

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Table 1. Patients' backgrounds

	Group I (n = 38)	Group II (n = 6)	Group III (n = 6)	Significance
Median age, years	55	58	56	NS
Range	31–72	43–63	50–66	
<i>Primary tumor</i>				
Location				NS
Right colon	7	0	0	
Transverse colon	2	0	0	
Left colon	14	3	3	
Rectum	15	3	3	
Differentiation				NS
Well	30	5	5	
Moderately	6	1	1	
Poorly	2	0	0	
Maximum diameter	6.9 ± 4.4	5.6 ± 1.6	4.3 ± 1.0	NS
Liver metastases, n	3.1 ± 2.8	5.2 ± 4.4	1.5 ± 2.1	NS
Distribution of liver metastases				
Solitary unilobar	14	2	4	
Multiple unilobar	15	0	1	
Multiple bilobar	9	4	1	
Time of diagnosis				NS
Synchronous	20	2	1	
Metachronous	18	4	5	
Surgical margin of clearance				NS
< 5 mm	32	4	3	
≥ 5 mm	6	2	3	
Extrahepatic disease				
Yes	2	0	1	NS
No	36	6	5	

NS = Not significant.

Patients and Methods

Between March 1978 and December 2004, 140 patients underwent 186 hepatectomies for hepatic metastasis of colorectal carcinoma at our department. Until 1996, lymph nodes around the hepatic pedicle, postpancreatic, common hepatic artery and celiac axis region were routinely dissected at the time of the first hepatectomy. Since 1990, lymph node dissection was done during hepatectomy only when nodes were palpable in the hepatic pedicle. Consistently, 50 patients who underwent node dissection during the initial and/or repeat hepatectomy were included in this study. Among 45 patients who underwent node dissection during initial hepatectomy, 38 had negative hilar node microscopically. Six patients had positive node at the initial hepatectomy. Five patients had positive nodes at repeat hepatectomy, and 1 had a positive node for the initial and repeat hepatectomies. These patients were divided into three groups: group I, 38 patients without hilar node metastasis; group II, 6 with hilar node metastasis at the initial hepatectomy, and group III, 6 with node metastasis at repeat hepatectomy. The patient who had a positive node in both of the initial and repeat hepatectomies was included in group III.

The 38 patients of group I comprised 12 women and 26 men with a median age of 55 years (table 1). The hepatectomy procedures were partial resection (non-anatomical wedge resection) in

8 patients, a sectionectomy in 2, right or left hepatectomy in 11, resection of segments IV, V and VIII in 2, and extended right or left hepatectomy in 15. The 6 patients in group II comprised 3 women and 3 men with a median of 58 years (table 2). The hepatectomy procedures were partial resection in 2, right hepatectomy in 3, and right trisectionectomy in 1. The 6 patients in group III comprised 4 women and 2 men with a median age of 56 years (table 3). The initial hepatectomy procedures were partial resection in 4, left lateral sectionectomy in 1, and resection of segments IV, V and VIII in 1. The repeat hepatectomy procedures were partial resection in 5 and right hepatectomy in 1. One patient underwent partial resection as a third hepatectomy later. Since 1 patient in group III had jaundice before the repeat hepatectomy, percutaneous transhepatic biliary drainage was performed. Another patient in group III showed intrahepatic bile duct dilatation on ultrasonic examination.

Statistical Analysis

The statistical evaluation of isolated variables in tumor characteristics was performed using the χ^2 test or Student's t test with the Mann-Whitney U test for multiple comparisons. The survival rate after surgery estimated by the Kaplan-Meier method was statistically analyzed using the log-rank test. Probabilities of <0.05 were considered to be statistically significant.

Table 2. Six patients with positive node metastasis at the initial hepatectomy (group II)

Pt. No.	Sex/age	Interval primary op. – hepatec.	Type of hepatectomy (number of foci)	Node metastasis sites	Recurrent sites	Survival after hepatectomy months
1	M/56	16 months	Right trisectionectomy (8)	Hepatic pedicle	Abdominal wall	1.5, dead (in-hospital death)
2	F/58	14 months	Right hepatectomy (1)	Hepatic pedicle	Liver, para-aortic nodes	20, dead
3	F/63	11 months	Right hepatectomy (1)	Hepatic pedicle	Liver, para-aortic nodes	13, dead
4	M/58	S	PR (2)	CHA, celiac trunk	Peritoneum, celiac axis	11, dead
5	M/62	50 months	PR (8)	CHA	Bones	8, dead
6	F/43	S	Right hepatectomy (11)	Hepatic pedicle, CHA	Liver, bones	8, dead

S = Synchronous; PR = partial resection (non-anatomical wedge resection) of the liver; CHA = common hepatic artery.

Table 3. Operation and sites of lymph node metastasis in repeat hepatectomy (group III)

Pt. No.	Sex/age	First hepatectomy (number of foci)	Disease-free interval between 1st & 2nd hepatectomy	2nd hepatectomy (number of foci)	Node metastasis sites	Survival after 1st hepatectomy, months
1	F/62	Left lateral sectionectomy (1)	28 months	PR (1)	Celiac trunk	68, dead
2	M/66	Resection of segments IV, V and VIII (2)	20 months	PR (1)	postpancreatic	75, dead
3	F/55	PR (7)	21 months	PR (3)	Hepatic pedicle	77, dead
4	F/57	PR (2)	20 months	Right hepatectomy Biliary reconstruction (2)	Hepatic pedicle	106, alive NED
5	M/50	PR (1)	8 months	PR, biliary reconstruction (8)	Hepatic pedicle	26, dead
6	F/52	PR (1)	7 months	PR (1)	Hepatic pedicle postpancreatic para-aortic	20, dead

PR = Partial resection of the liver; NED = no evidence of disease.

Results

Patients' Backgrounds

Although the ages, locations and differentiation of primary tumors, number of liver metastases, maximum diameters of the liver tumors, distributions of metastatic nodules in the livers, times of diagnosis (synchronous or metachronous metastasis), surgical margins of clearance and presence of extrahepatic disease were analyzed, there were no significant differences in each variable among the three groups (table 1).

Postoperative Complications

Postoperative complications occurred in 14 of 50 patients (28%), including bile leakage from the liver stump

in 5 patients, anastomotic leakage in 1 and wound infection in 8. There were no significant differences in the occurrence of complications among the groups.

Sites of Node Metastasis

In group II, 4 patients had metastasis in the hepatic pedicle, 3 along the common hepatic artery, and 1 along the celiac trunk (table 2). In group III, 4 patients had metastasis in the hepatic pedicle, 2 in the posterior portion of the pancreatic head, 1 along the common hepatic artery, and 1 in the para-aortic region (table 3). One patient in group III (patient No. 1), who had node metastasis at both initial and repeat hepatectomies, had a positive node along the left gastric artery at the initial hepatectomy and along the celiac trunk at repeat hepatectomy. Node metas-

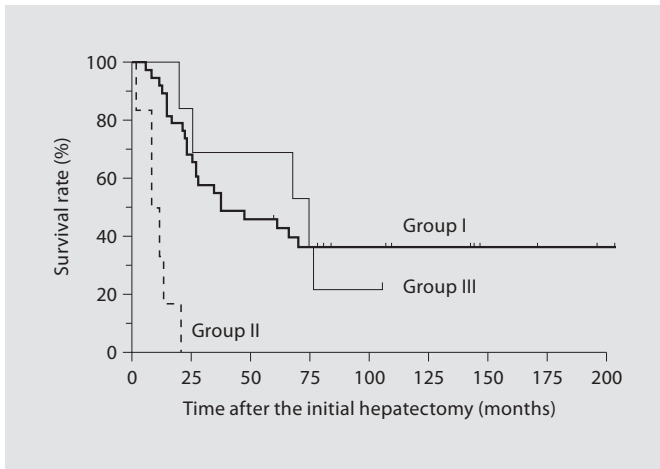


Fig. 1. Survival curves after the initial hepatectomy for group I (38 patients without hilar node metastasis at the initial hepatectomy), group II (6 with node metastasis at the initial hepatectomy) and group III (6 with node metastasis at repeat hepatectomy). A significant statistical difference was observed between group I and group II ($p < 0.01$).

tasis along the left gastric artery appeared to have metastasized from a nodule in the left lateral segment. There were no significant differences in frequency of sites of the node metastases between groups II and III.

Prognosis

The 1-, 3-, and 5-year survival rates of group I, the patients without lymph node metastasis, were 90, 55, and 46%, respectively (fig. 1). The 1-year survival rate of group II was 33%, and all patients in this group died of recurrence of carcinoma within 2 years (fig. 1, table 2). The patient who died of hepatic failure 45 days after massive hepatectomy (estimated residual volume of 17%) also had a metastatic nodule in the abdominal wall on autopsy (table 2). There was, therefore, a significant difference in the survival rates between groups I and II ($p < 0.01$).

In group III, there were 4 patients who survived for more than 5 years after the initial hepatectomy, patients No. 1–4 (table 3). Of note, recurrent liver metastases were found after more than 20 months in long-term survivors. In contrast, the survival periods from initial hepatectomy were 20 and 26 months when recurrent liver tumors were found within 12 months for patients No. 5 and 6 (table 3). In particular, patient No. 6 with para-aortic lymph metastasis died of disseminated lymph metastasis after 10 months of repeat hepatectomy with lymphadenectomy.

Patients Who Underwent Biliary Reconstruction

Metastatic nodes invaded the extrahepatic bile duct but not liver parenchyma in 2 patients in group III. One patient had invasion of the metastatic node to the middle third of the extrahepatic bile duct, and the lesion was treated by resection of the extrahepatic bile duct and partial hepatectomy (No. 5 in table 3). Metastasis was thereafter noted in the right lung. The doubling time of a pulmonary nodule was 73 days on a plain chest X-ray. On the other patient, right hepatectomy including extrahepatic bile duct resection was performed for two nodules in the liver and node metastasis, and the patient has been doing well without recurrence of the disease for 7 years after the repeat hepatectomy. On both patients, biliary tract reconstruction was performed using a jejunal loop.

Discussion

Metastasis to the hilar node from colorectal liver metastasis was defined as ‘remetastasis’ by August et al. [8]. The prevalence of hepatic node metastasis from colorectal liver metastasis ranges from 11.5 to 27.3% [1, 6, 9–12]. Such node metastasis is frequently seen in the hepatic pedicle or around the common hepatic artery. It is believed that colorectal liver metastasis with hilar node ‘remetastasis’ should be regarded as extrahepatic disease. Patients with hilar nodal lesion from liver metastasis have been excluded from the indication for surgical removal [4, 5, 13]. However, node dissection should be applied to some limited cases, since the morbidity of regional node dissection with hepatectomy is as low as that of hepatectomy alone [10], and several long-term survivors of such surgery have been reported [14, 15].

The 5-year survival rate of patients with hilar negative node were previously reported as 22–50% [9, 14]. Consistent with these, in the present study, the 5-year survival rate of patients without hepatic node metastasis (group I) was 46%. This was significantly better than for the patients with hepatic positive node at initial hepatectomy (group II). Thus, node dissection may not contribute to prolonging the survival of patients with node metastasis at initial hepatectomy. However, in spite of the presence of hilar node metastasis, the prognosis of patients who underwent repeat hepatectomy was satisfactory only when recurrent liver tumors were found more than 12 months after the initial hepatectomy in the present study. The observation that the patient with extrahepatic biliary obstruction secondary to hepatic pedicle node metastasis survived without recurrent disease for 7 years after repeat hepatectomy

(patient No. 4 of group III) contrasts with the findings that the prognosis is poor if such patients receive palliative treatment [16–18]. At the moment, it remains unclear why a prolonged duration between the initial and repeat hepatectomies is correlated with a better prognosis. We speculate that a tumor showing a longer disease-free interval may be a slow-growing type as suggested by Que et al. [19]. Therefore, aggressive repeat hepatectomy including node dissection for patients with hepatic node metastasis may contribute to prolonged survival, when the disease-free interval from the initial to repeat hepatectomy is more than 12 months. Further studies would be required to reveal more clearly the clinical benefit of repeat hepatectomy including lymph node dissection for patients with hepatic node metastasis, because our study was performed with a short patient series under non-randomized control trials.

The site of lymph node metastasis may be an important factor that influences the prognosis after hepatectomy plus regional lymphadenectomy. Jaeck et al. [20] divided perihilar lymph nodes into two parts: area 1, hepatic pedicle and postpancreatic lymph nodes, and area 2, lymph nodes along the common hepatic artery and celiac trunk. In their study, the 3-year survival was 38% if lymph node metastasis was limited within area 1, whereas no patient with area 2 involvement survived longer than 1 year [20]. Consistent with their report, lymph node metastasis was limited within area 1 in 3 of 4 long survivors in our series. Our patient with node metastases around the aorta (No. 6 of group III) developed disseminated lymph metastasis within 2 months after repeat hepatectomy with lymphadenectomy and died 8 months later. Therefore, repeat hepatectomy plus node

dissection is a promising surgical treatment when lymph involvement is limited within area 1 [20].

Our most recent policy on operative indications for patients with colorectal liver metastasis is as follows: if there is no metastasis at hepatic regional nodes on preoperative examinations, we make plans for an initial hepatic resection. If we palpate the enlarged nodes in the hepatic pedicle and/or along the common hepatic artery by palpation during operation, we perform sampling of them. When metastasis is confirmed by intraoperative pathological examination, hepatic resection is canceled. If the disease-free interval is more than 12 months and node metastasis is limited to the hilar or postpancreatic nodes in candidates for repeat hepatectomy, regional node dissection will be performed. Patients with node metastasis in the common hepatic artery area or more distant area are contraindicated for surgery.

Conclusion

In conclusion, repeat hepatectomy with regional node dissection may be indicated when the disease-free interval between first and second hepatectomy is more than 12 months, and node metastasis is limited within the hepatic pedicle and postpancreatic area.

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