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ORIGINAL ARTICLE

Surgical treatment of lymph node metastases from hepatocellular carcinoma

Shin Kobayashi · Shinichiro Takahashi · Yuichiro Kato · Naoto Gotohda · Toshio Nakagohri · Masaru Konishi · Taira Kinoshita

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Abstract
Background No consensus has been reached on the feasibility and efficacy of surgery for lymph node metastases (LNM) from hepatocellular carcinoma (HCC).
Methods Of 2189 patients with HCC treated at our hospital between July 1992 and March 2008, we retrospectively reviewed the medical dossiers of the 18 patients (0.8%) who underwent lymph node resection and were pathologically diagnosed to have LNM from HCC. The surgical procedure for LNM was selective lymphadenectomy of those lymph nodes suspected to harbor metastasis. The feasibility and efficacy of selective lymphadenectomy was examined, and clinicopathological factors were analyzed with the aim of determining which patients would most benefit from surgery.
Results Eighteen patients underwent surgery without mortality or liver failure. Morbidities were found in four patients (22.2%). The median survival time (MST) after surgery was 29 months [95% confidence interval (CI) 21–38 months). The 1-, 3-, and 5-year overall survival rates were 85, 42, 21%. The median progression-free survival (PFS) after surgery was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months). Single LNM was the only favorable prognostic factor after surgery (Hazard ratio 0.082, 95% CI 0.008–0.83).
Conclusion Selective lymphadenectomy of LNM from HCC was a feasible and efficacious procedure. Survival rates can be expected to improve after selective lymphadenectomy of single LNM.

Keywords Hepatocellular carcinoma · Lymph node metastases · Surgery

S. Kobayashi · S. Takahashi (✉) · Y. Kato · N. Gotohda · T. Nakagohri · M. Konishi · T. Kinoshita
National Cancer Center East Hospital,
6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
e-mail: shtakaha@east.ncc.go.jp

Introduction

Lymph node metastases (LNM) are rare and generally associated with poor prognosis in hepatocellular carcinoma (HCC) [1, 2]. No consensus has yet been reached on the treatment strategy for LNM from HCC [3–5]. A few case reports have been published on the surgical treatment of LNM from HCC. Abe et al. [6] described two patients who survived for more than 4 years after the resection of an isolated metastatic lymph node followed by transarterial embolization (TAE). Togo et al. [7] also described a patient who survived for 7 years without recurrence after single node resection and simultaneous hepatectomy. In contrast, Uenishi et al. [8] reported that the resection of multiple LNM led to a poor prognosis, and they questioned the efficacy of regional lymphadenectomy in HCC. Their poor results are partly attributable to the deterioration of cirrhotic liver function due to altered portal or lymphatic drainage caused by extensive LN dissection [9]. Based on these findings, it is possible that selective lymphadenectomy of suspected metastatic lymph nodes instead of regional lymphadenectomy would be an effective treatment for LNM from HCC.

The aims of this study were to present our surgical experiences on LNM from HCC and to discuss the feasibility and efficacy of selective lymphadenectomy. We also

examined prognostic factors to determine who might most benefit from surgical resection.

Patients and methods

From July 1992 to March 2008, 2189 patients with HCC were treated at the National Cancer Center Hospital East in Kashiwa, Japan. Among those 2189 patients with HCC, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC and 21 patients (1.0%) actually underwent surgery. Eighteen patients (0.8%) who underwent lymph node resection and in whom LNM were pathologically diagnosed were included in this and their medical histories retrospectively examined.

The staging and resectability of tumors were assessed by contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic arterial angiography, ultrasounds, and chest X-rays. The clinical diagnosis of LNM was based on the following findings from the contrast-enhanced CT, MRI, or ultrasound scans: (1) the short axis diameter of the lymph node was minimally >1 cm; (2) the lymph node showed hypervascularity in the arterial phase and washout of enhancement in the venous phase; (3) the liver tumor had been pathologically or clinically diagnosed as HCC according to the guidelines issued by American Association for the Study of Liver Diseases [10]. A typical case of LNM from HCC is depicted in Fig. 1. Indications of surgery for LNM from HCC were: (1) isolated LNM; (2) metachronous LNM without any tumor in the liver or synchronous LNM with intrahepatic tumor that was potentially resectable or controllable by non-surgical treatments, such as TAE or radiofrequency ablation (RFA); (3) no extrahepatic metastases except lymph nodes; (4) sufficient liver function (Child–Pugh grade [11]: A or B) and performance status [Eastern Cooperative Oncology Group Performance Status (ECOG PS) [12]: 0 or 1] to undergo surgery. Liver function was assessed by liver biochemistry tests, the Child–Pugh grade, and the indocyanine green retention rate at 15 min [13]. The patients' data were reviewed by hepatic surgeons, medical oncologists, and interventional radiologists during a conference to determine if the patients met the aforementioned criteria.

Fig. 1 Computed tomography findings of a solitary lymph node metastasis from hepatocellular carcinoma (HCC). A round-shaped, large lymph node (*arrowhead*) was found on the posterior surface of pancreas head (*arrow*). The lymph node was 6.0 cm in diameter and showed early enhancement in the arterial phase of the dynamic study

The surgical treatment procedure for LNM was, in principle, selective lymphadenectomy in which only lymph nodes suspected of metastasis were resected. With this approach, potential deterioration of liver function caused by altered lymphatic drainage after extensive LN dissection was avoided. Thin vessels around the lymph nodes were ligated whenever possible to prevent lymphatic leakage. Resected lymph nodes were pathologically examined with hematoxylin–eosin (HE) stain. When the results from the HE stain were not definitive, we also performed immunohistochemistry tests to confirm the diagnosis. Patients were followed-up every 3 months after surgery and were assessed for recurrence by CT examination and tumor marker level (alpha fetoprotein and protein induced by vitamin K absence-II).

Survival time was calculated from the date of operation. Clinicopathological findings and survival were compared among the 18 patients who underwent resection for LNM. The correlation between survival and clinicopathological findings was also examined. Survival analyses were performed using the Kaplan–Meier method, and differences between the curves were tested using the log-rank test (SPSS ver. 11.0J for Windows; SPSS, Chicago, IL). Factors related to survival were analyzed with the Cox proportional hazards regression model. p values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Patient characteristics of the 18 patients are listed in Table 1. Sixteen and two patients were Child–Pugh grade A and B, respectively. The LNM was solitary in 13 patients and multiple in five patients. The mean diameter of the metastatic lymph nodes was 5.1 cm. Thirteen patients had received previous treatments that consisted of hepatectomy ($n = 8$), TAE ($n = 3$), percutaneous ethanol injection ($n = 1$), and proton-beam therapy ($n = 1$). Median

Table 1 Patient characteristics

Patient characteristics	Patients ($n = 18$)
Male, *n* (%)	16 (88.9)
Age (years)	65.2 ± 2.1
Performance status (0/1/2/3), *n*[a]	17/1/0/0
HCV Ab (+), *n* (%)	9 (50)
Child–Pugh grade (A/B/C), *n*	16/2/0
Albumin (g/dl)	3.9 ± 0.1
T.Bil (mg/dl)	0.9 ± 0.1
ICG15R (%)	17.3 ± 2.6
PT (% standard)	82.6 ± 3.9
Platelet ($\times 10^4$/mm^3)	15.3 ± 1.1
AFP (ng/ml)	1200 ± 750
PIVKA-II (mAU/ml)	410 ± 270
Previous treatments, *n* (%)	13 (72.2)
Simultaneous intrahepatic lesion, *n* (%)	13 (72.2)
Portal vein invasion, *n* (%)[b]	8 (44.4)
Multiple intrahepatic lesions, *n* (%)[b]	7 (38.9)
T-stage of intrahepatic lesions (T1/T2/T3/T4), *n*[b,c]	3/5/5/5
Size of LNM (cm)	5.1 ± 1.0
Multiple LNM, *n* (%)	5 (27.8)
Extrahepatic metastasis except LNM, *n* (%)	0 (0)
JIS score (3/4/5), *n*[d]	16/2/0

All values are given as the standard error of the mean (SEM) unless otherwise indicated

HCV Ab Hepatitis C virus antibody, *T.Bil* total bilirubin, *ICG15R* indocyanine green retention rate at 15 min, *PT* prothrombin time, *AFP* alpha fetoprotein, *PIVKA-II* protein induced by vitamin K absence-II, *LNM* lymph node metastases, *JIS score* Japan Integrated Staging score

[a] Performance status was evaluated according to the ECOG (Eastern Cooperative Oncology Group) criteria [11]

[b] When LNM was metachronous and the hepatic lesion did not exist simultaneously, the findings were evaluated for the most recently treated hepatic lesions

[c] T-stage was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[d] Japan Integrated Staging score can be obtained by combining the TNM stage score by the Liver Cancer Study Group of Japan and the Child–Turcotte-Pugh stage score [18]

duration from the primary treatment for HCC to LN recurrence in these 13 patients was 36 months (range 4–124 months). In 13 patients, LNM were accompanied by simultaneous hepatic lesions, and five of the 13 patients had multiple hepatic lesions. Of the five patients without simultaneous hepatic lesions, two had multiple hepatic lesions previously while three patients had only single lesions. The underlying liver pathology in three patients was normal, while seven patients had chronic hepatitis and eight patients had cirrhosis.

Locations of LNM

The metastatic lymph nodes in the 18 patients were located along the left gastric artery ($n = 4$), on the posterior surface of the pancreas head ($n = 4$), around the abdominal aorta ($n = 3$), above the diaphragm ($n = 3$), in the hepatoduodenal ligament ($n = 3$), and along the common hepatic artery ($n = 1$).

Surgery for LNM

Selective lymphadenectomy was performed in 17 patients, while one patient underwent regional lymphadenectomy along the left-gastric artery, common hepatic artery, and hepatoduodenal ligament. Among the 13 patients with simultaneous hepatic lesions, nine patients underwent simultaneous hepatectomy (3 lobectomies, 3 partial resections, 1 segmentectomy, 1 central bisegmentectomy, and 1 extended lobectomy), three patients received non-operative treatments (2 TAE and 1 RFA), and one patient received careful follow-up without treatment because the lesion became obscure in severely cirrhotic liver and could not undergo TAE. During the same period, one patient underwent surgery for LNM, but the lymph node could not be resected due to involvement of main portal vein. Two other patients underwent surgery for LNM, but the pathological findings revealed that one was benign reactive lymphadenopathy and the other was metastasis from a neuroendocrine tumor. These three cases were not included in the present study. There was no postoperative mortality. Six postoperative complications occurred in four patients: transient pleural effusions ($n = 2$), cholecystitis ($n = 1$), bile leak ($n = 1$), intestinal obstruction ($n = 1$), and wound infection ($n = 1$). No patients developed liver failure or refractory ascites. Transient pleural effusions were treated with single thoracocentesis.

Survival

The median survival time (MST) of 18 patients was 29 months after surgery [95% confidence interval (CI) 21–38 months) and 32 months after clinical diagnosis (95% CI 23–41 months). The 1-, 3-, and 5-year overall survival rates after surgery were 85, 42, 21%, respectively. The median progression-free survival (PFS) after surgery for LNM was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months) (Fig. 2).

Recurrence after resection of LN metastasis from HCC

Among the 12 patients with disease progression after surgery, four patients developed only intrahepatic lesions that were treated by TAE ($n = 2$) or RFA ($n = 2$). The other

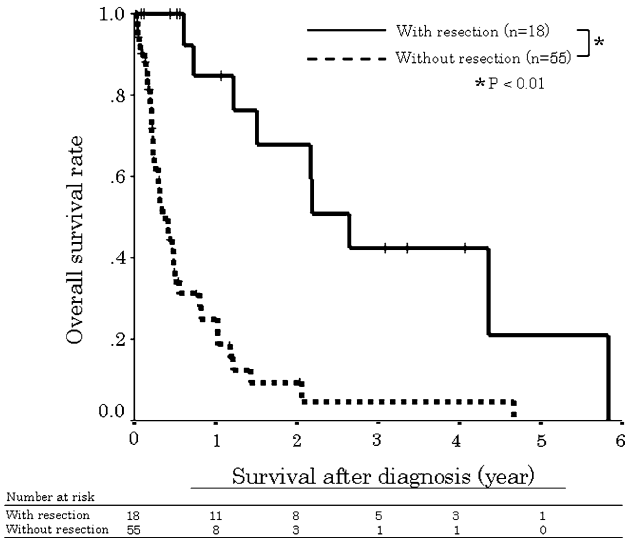

Fig. 2 Cumulative survival curves of patients with or without resection of lymph node metastases (LNM). The median survival time after clinical diagnosis was 32 months with resection (95% CI 23–41 months) and 4 months without resection (95% CI 3–6 months)

eight patients developed both intra- and extrahepatic lesions. The extrahepatic recurrences occurred in LN ($n = 6$), lung and LN ($n = 1$), and peritoneum ($n = 1$). One patient with lung and LN recurrence was treated with repeated selective lymphadenectomy and partial lung resection each time. The remaining seven patients with extrahepatic recurrences received the best supportive care ($n = 4$) or chemotherapy ($n = 3$).

Correlation between clinicopathological factors and overall survival

The correlation between clinicopathological factors and overall survival of the 18 patients is shown in Table 2. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (MST: 52 vs. 14 months after surgery, $p < 0.01$) (Fig. 3). Liver functions, status of viral hepatitis, history of previous treatments, presence of intrahepatic lesions, curability of simultaneous intrahepatic lesions, regions of metastatic LNs, and other factors were not statistically significant. In order to eliminate the effect of possible confounding factors and small sample size, factors with p values <0.2 by univariate analysis were analyzed with the Cox proportional hazards regression model: the single LNM was found to be the only favorable prognostic factor (hazard ratio 0.082, 95% CI 0.008–0.83).

Non-surgical treatments

During the same period, 55 patients were clinically diagnosed to have LNM, but did not undergo lymphadenectomy due to the following reasons: (1) poor control of intrahepatic lesions ($n = 18$); (2) regional or systemic LNM ($n = 16$); (3) extrahepatic metastasis other than LNM ($n = 9$); (4) poor liver function (Child–Pugh grade C) ($n = 5$); (5) poor performance status (ECOG PS ≥ 2) ($n = 4$); (6) patients' preference ($n = 2$); (7) involvement of main portal vein ($n = 1$). The MST of 55 patients without lymphadenectomy was 4 months after clinical diagnosis (95% CI 3–6 months) and was significantly shorter than that of patients with lymphadenectomy (32 months; 95% CI 23–41 months) ($p < 0.01$) (Fig. 2). Non-operative treatments included the best supportive care ($n = 19$), systemic chemotherapy ($n = 13$), TAE ($n = 8$), external beam radiation therapy ($n = 5$), transarterial infusion chemotherapy ($n = 5$), immunotherapy ($n = 3$), and hepatic arterial continuous infusion chemotherapy ($n = 2$). Four patients developed complications that were directly related to the LNM from HCC, namely, obstructive jaundice ($n = 2$), esophageal obstruction ($n = 1$), and obstruction of inferior vena cava ($n = 1$) (Fig. 4).

Discussion

Lymph node metastases from HCC are rare. The feasibility and efficacy of surgical treatment for LNM from HCC has not been fully evaluated. Several case studies have reported mortality cases and high morbidity rate after surgery [8, 9]. In our study, however, there was no mortality or liver failure associated with surgery for LNM, although eight cases were complicated by liver cirrhosis. These results demonstrate the safety of selective lymphadenectomy for LNM from HCC in selected patients and are in contrast to the high rate of liver failure previously reported following regional lymphadenectomy [8, 9]. The favorable outcomes of selective lymphadenectomy may be attributable to the maximum conservation of the lymphatic and portal flow around the liver. Selective lymphadenectomy of LNM might be a safer and feasible procedure in patients with liver cirrhosis, although the indication for selective lymphadenectomy should still be carefully considered, especially in terms of liver function.

Considering the survival benefit of selective lymphadenectomy for patients with LNM, the MST was 29 months after lymphadenectomy and the 1-, 3-, and 5-year OS were 85, 42, and 21%. Survival more than 3 years was achieved in five patients after surgery, and two of these patients are still alive without a recurrence. These results indicate the survival benefit of selective lymphadenectomy for LNM from HCC in selected patients. The efficacy of lymphadenectomy was recently questioned by Sun et al. [3]. However, the methods and patient backgrounds were different between two studies. In Sun's study, the evaluation

Table 2 Correlation between clinicopathological factors and overall survival after lymph node resection of HCC (the log-rank test)

Patient characteristics	*n*	Univariate analysis				Multivariate analysis		
		3-year OS (%)	5-year OS (%)	MST (months)	*p* value	Hazard ratio	(95% CI)	*p* value
Age (years)								
<70	12	34.3	0	24.5	0.15	0.09	(0.005–1.62)	0.29
≧70	6	66.7	66.7	68.3				
Serology of viral hepatitis								
HBs Ag (−) and HCV Ab (−)	5	100	0	52.3	0.13	0.02	(0.00–1.12)	0.19
HBs Ag (+)/HCV Ab (+)/both (+)	13	22.2	22.2	24.5				
Child–Pugh grade								
A	16	40.9	0	29.4	0.48			
B	2	50	50	24.5				
AFP (ng/ml)								
≥400	5	50	50	14.5	0.97			
<400	13	38.1	19.1	29.4				
PIVKA-II (mAU/ml)								
≥100	9	40	40	29.4	0.77			
<100	9	41.7	41.7	24.5				
Liver cirrhosis								
Yes	8	57.1	57.1	68.3	0.18	0.04	(0.00–5.73)	0.07
No	10	22.2	0	25.6				
Simultaneous hepatic lesions								
Absent	5	75	75	68.3	0.08	0.57	(0.00–88.8)	0.21
Present	13	25.9	0	25.6				
Number of intrahepatic lesions[a]								
Single	12	37.5	37.5	24.5	0.6			
Multiple	6	50	25	25.6				
T-stage of intrahepatic lesions[b]								
T1/2	8	33.3	33.3	24.5	0.67			
T3/4	10	51.4	25.7	52.3				
Portal vein invasion[a]								
Present	8	62.5	0	52.3				
Absent	10	28.6	28.6	25.6	0.77			
Number of LNM								
Single	13	55.6	27.8	52.3	<0.01	0.082	(0.008-0.83)	0.03
Multiple	5	0	0	14.5				
Size of metastatic LN (cm)								
≥4.0	12	33.3	16.7	25.6	0.48			
<4.0	6	66.7	66.7					
Differentiation of metastatic LNs								
Well or moderately differentiated	3	50	50	25.6				
Poorly differentiated	15	40.9	20.5	29.4	0.68			
JIS score[c]								
3	16	40.9	0	29.4	0.48			
4 or 5	2	50	50	24.5				

HCC Hepatocellular carcinoma, *OS* overall survival, *MST* median survival time, *CI* confidence interval, *LN* lymph node, *HBs Ag* hepatitis B surface antigen

[a] Metachronous intrahepatic lesions were evaluated in the absence of simultaneous intrahepatic lesions

[b] T-stage of intrahepatic lesions was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[c] Japan Integrated Staging score can be obtained by combination of the TNM stage score by the Liver Cancer Study Group of Japan and the Child-Turcotte-Pugh stage score [18]

of LNM and decision whether lymphadenectomy should be done or not were mostly based on the palpation of surgeons during surgery. The preoperative evaluation of LNM was not performed precisely in most of the patients. In comparison, in our study, the diagnosis of LNM was made by preoperative imaging diagnosis. Selective lymphadenectomy was performed only for lymph nodes which were clinically diagnosed for metastasis. Patients' backgrounds were also different because the present study included many recurrent cases and cirrhotic cases. Based on these aspects, we consider that the efficacy of resection for LNM from HCC was not fully evaluated in Sun's study and that selective lymphadenectomy is a safe and beneficial procedure in selected patients.

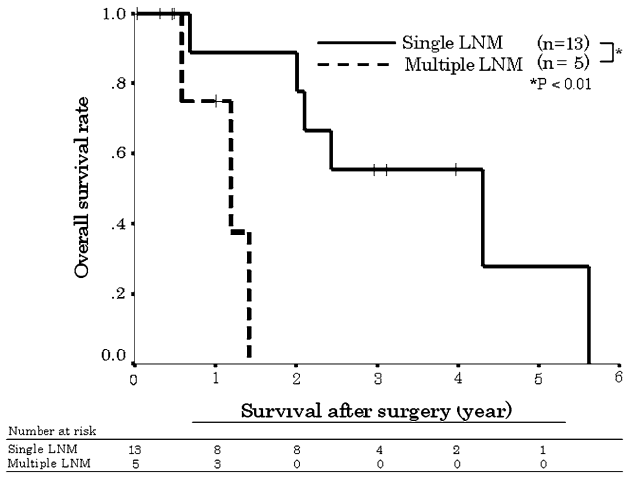

Fig. 3 Cumulative survival curves after surgery according to the number of MLN. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (mean survival time 52 vs. 14 months; $p < 0.01$)

The possible candidates for selective lymphadenectomy are not many. In the present study, among 2189 patients with HCC who were treated in our institution, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC, and 21 patients (1.0%) actually underwent surgery according to the aforementioned criteria. Among those 21 patients, 19 patients were pathologically diagnosed to have LNM from HCC while benign reactive lymphadenopathy was identified in resected lymph nodes in one case and metastasis from neuroendocrine tumor in the other. The positive predictive value of our diagnostic criteria of LNM from HCC was 90.5%. Among 19 patients with pathologically proven LNM, 18 patients underwent successful lymphadenectomy while it was abandoned due to invasion of the main portal vein in one patient. Thus, selective lymphadenectomy might be indicated in 24.0% (18/75) of cases with clinical diagnosis of LNM from HCC.

A comparison of surgical and non-surgical treatments suggests that external beam radiation therapy can be considered as a possible alternative modality for the treatment of LNM from HCC. However, median survival following this therapy has been found to be only 7–9.4 months, while the incidence of gastrointestinal bleeding was fairly high (9.4–22.0%) [4, 15]. A newer molecular targeting agent, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Basel, Switzerland/Onyx Pharmaceuticals, Emeryville, CA), has been recently shown to prolong survival in patients with advanced HCC [16, 17]. However, a survival benefit was not demonstrated in the sub-group analysis of patients with extrahepatic metastasis. Long-term survival was rarely seen after those non-surgical treatments. Although candidates for resection are limited, and multimodal treatment might be necessary after resection, surgery for LNM seems to play an important role in achieving

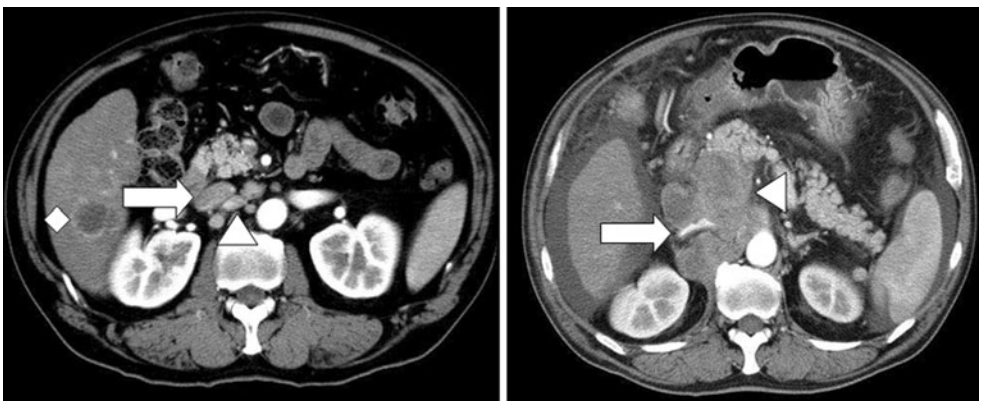

Fig. 4 Computed tomography findings of inferior vena cava obstruction by huge metastatic lymph nodes from hepatocellular carcinoma. *Left* A 57-year-old female underwent proton beam therapy for her solitary HCC (*diamond*). The slightly enlarged lymph nodes (*arrowhead*) around the inferior vena cava (IVC) (*arrow*) were at first judged equivocal as metastases (short axis diameter <1.0 cm). *Right* Only 2 months later, the patient developed IVC obstruction (*arrow*) by the rapidly growing lymph nodes (*arrowhead*)

long-term survival in the treatment strategy for LNM from HCC.

Evaluating the correlation between clinicopathological factors and prognosis after selective lymphadenectomy, single LNM was the only favorable prognostic factor after surgery (hazard ratio 0.082, 95% CI 0.008–0.83). The MST of patients with single and multiple LNM after surgery were 52 and 14 months, respectively ($p < 0.01$). All five patients who survived >3 years had single LNM and four of them did not develop extrahepatic metastasis within 3 years. On the contrary, three of the five patients with multiple LNM developed intra- and extrahepatic recurrences within 6 months after surgery. Therefore, multiple LNM indicated its advanced and systemic nature of the disease, while single LNM might be considered to be a localized disease. The MST of patients with resection of multiple LNM was not significantly longer than that of patients without resection (15 vs. 4 months after diagnosis, respectively; $p = 0.12$). Patients with single LNM appear to be the best candidates for selective lymphadenectomy. On the other hand, efficacy of selective lymphadenectomy for multiple LNM seemed equivocal due to its advanced and systemic nature of the disease.

The LNM from HCC might also cause severe complications, such as obstructive jaundice, pyloric obstruction, and inferior vena cava obstruction [15]. The resection of LNM might prevent these complications. In our institution, there were four complications directly related to LNM during the same period as that covered by our study. One patient developed inferior vena cava obstruction due to rapidly growing lymph nodes while receiving proton beam therapy for her solitary intrahepatic lesion (Fig. 4). Another patient developed esophageal obstruction due to large metastatic lymph nodes in the mediastinum. Two other patients developed obstructive jaundice due to metastatic lymph nodes in the hepatoduodenal ligament, which were treated with percutaneous transhepatic biliary drainage. Although selective lymphadenectomy should be performed with curative intent, it might additionally be beneficial as a preventative and palliative measure against these life-threatening complications.

The present study has several limitations. It is a single institutional study with a small patient population. Also, this study was not performed as a randomized controlled trial (RCT). However, RCTs are very difficult to conduct in this disease group due to the small number of patients scattered over diverse facilities. Our future perspective is to conduct a prospective observational study in a multi-institutional setting focusing on selective lymphadenectomy for patients with single LNM.

Conclusion

Selective lymphadenectomy of LNM from HCC is a feasible and efficacious procedure. Long-term survival can be expected after selective lymphadenectomy, especially in patients with a single LNM.

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