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Lymphadenectomy Combined with Locoregional Treatment for Multiple Advanced Hepatocellular Carcinoma with Lymph Node Metastases

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ABSTRACT

Lymphadenectomy of lymph node metastasis (LNM) from hepatocellular carcinoma (HCC) may potentially improve survival of patients with intrahepatic tumors controllable by means of locolegional treatment. However, the treatment strategy has not gained wide clinical acceptance, especially in patients with multiple advanced HCC. Thus, the purpose of this study is to evaluate the role of lymphadenectomy combined with locoregional treatment for the management of multiple advanced HCC with LNM.

Between January 1998 and August 2012, 15 patients underwent a selective lymphadenectomy either concurrently or sequentially after hepatectomy. Seven of 15 patients underwent reductive hepatectomy while the remaining 8 patients had hepatectomy at curative intent. In patients with reductive hepatectomy, lymphadenectomy was concurrently performed and the residual intrahepatic tumors were treated thereafter with additional locoregional treatments consisting of transcatheter arterial chemoembolization, radiofrequency ablation, and percutaneous isolated hepatic perfusion.

Only 4 patients (26.6%) of 15 patients developed lymph node recurrence. However, intrahepateic recurrence was encountered in 13 of 15 patients. The median survival time after lymphadenectomy was 25.2 months with the overall survival rates at 1, 2, and 3 years being 76.9%, 52.7%, and 26.4%, respectively. Selective lymphadenectomy and multimodal locoregional treatment in patients with multiple residual tumors exhibited a similar overall survival to complete resection of LNM and intrahepatic tumors (P=0.78).

Lymphadenectomy combined with an additional aggressive locoregional treatments may be justified in selected patients with multiple advanced HCC with LNM

ABBREVIATION

HCC, hepatocellular carcinoma; LNM, lymph node metastases;
RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization;

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PIHP, percutaneous isolated hepatic perfusion; AFP, alpha-fetoprotein;
PIVKA II, protein induced by vitamin K absence or antagonist-II.

INTRODUCTION

Lymph node metastasis (LNM) is not common in patients with hepatocellular carcinoma (HCC) as compared to other malignant diseases(1, 8), for which regional lymph node dissection is routinely practiced as an essential part of radical surgery(6, 15, 22). According to the Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan, the incidence of LNM in patients treated with hepatectomy was approximately 1.2% based on preoperative diagnostic imaging studies, and only 0.9% in histology(8). This could be explained by the fact that patients with HCC and LNM frequently have multiple intrahepatic tumors which generally preclude surgical intervention(2, 12, 25, 27). Several groups have described a slightly higher incidence of LNM from HCC ranging from 5.1% to 7.5% based on prophylactic lymph node dissection concurrently performed during hepatectomy(5, 23, 30). These studies have agreed that LNM was uniformly a poor prognostic factor, and prophylactic lymphadenectomy does not contribute to overall survival (OS) of patients with HCC.

The Liver Cancer Study Group of Japan has been concluding nationwide surveys of patients with HCC. But the data concerning HCC patients with histologically proven LNM has not been accumulated. Meanwhile, some paper reported that the median survival time (MST) of patients with LNM from HCC was limited approximately 6 months in the natural history(23). The MST with systemic chemotherapy for patients with LNM ranged from 5.6 to 10.7 months, and those with radiation therapy were in the range of 7 to 14.7 months(13, 14, 16, 17, 21, 29, 31, 33, 34). Therefore, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Basel, Switzerland / Onyx Pharmaceuticals, Emeryville, CA) is currently the only recommended therapeutic option for advanced HCC with LNM in the European Guideline(3). Although advanced HCC with LNM generally preclude surgical treatments, lymphadenectomy of LNM has been advocated to date by several investigators(7, 9, 19, 24, 26, 28). The candidates to surgical resection in these studies were strictly limited for those with metachronous, solitary LNM without intrahepatic tumors or with intrahepatic tumors potentially controllable by the standard therapeutic options. Thus, the role of lymphadenectomy of LNM remains unknown in the majority of patients with LNM.

We have shown that percutaneous isolated hepatic perfusion (PIHP) is a potent locoregional treatment for patients with multiple intrahepatic tumors(10). In addition, reductive hepatectomy followed by PIHP produced a strong antitumoral effect on multiple advanced HCC, when liver function allows this concentrated treatment approach(11). Taken together, we have introduced an aggressive multimodal treatment strategy combining PIHP for multiple advanced HCC and surgical resection of LNM.

The aim of this study is to report a pilot study on lymphadenectomy combined with aggressive locoregional treatments as represented by reductive hepatectomy followed by PIHP in patients with multiple advanced HCC and LNM

MATERIALS AND METHODS

Patients

Between January 1998 and August 2012, 598 patients with HCC underwent surgical treatment at our institution. Among them, all patients with resectable LNM were listed to our trial. Resectable LNM were considered as follows; (1) isolated LNM; (2) solitary or a few

number of LNM; (3) no distant matastasis except lymph nodes (4) sufficient liver function for surgical operation; (5) metachronous LNM or synchronous LNM with controllable intrahepateic tumors. It is particularly worth noting that extensive intrahepatic tumors such as multinodular and bilobar distribution were not contraindication in our strategy. If the distribution and extent of the intrahepatic tumors did not allow complete surgical removal, we selected lymphadenectomy on a priority basis and reductive hepatectomy was added at the first stage. The residual intrahepatic tumors were treated subsequently at the second stage with additional locoregional treatments consisting of percutaneous radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and PIHP in an optimal combination. We set a base date at the point of first diagnosis of HCC and defined synchronous / metachronous LNM. A typical case of two-stage treatment is shown in Fig.1. Six of 15 patients had synchronous LNM, while other 9 patients had metachronous LNM. All patients were followed every three months until death or until 2012 December. All fifteen patients were divided to 2 groups (group A/B) by presence or absence of residual intrahepatic tumors after lymphadencetomy. Patients belonging to group A underwent a two-stage procedure. In the group B, complete surgical clearance of LNM and intrahepatic tumors were simultaneously done. In term of host, tumor and LNM factors, characteristic of patients in group A and B were compared. And the therapeutic result of group A and B were also compared.

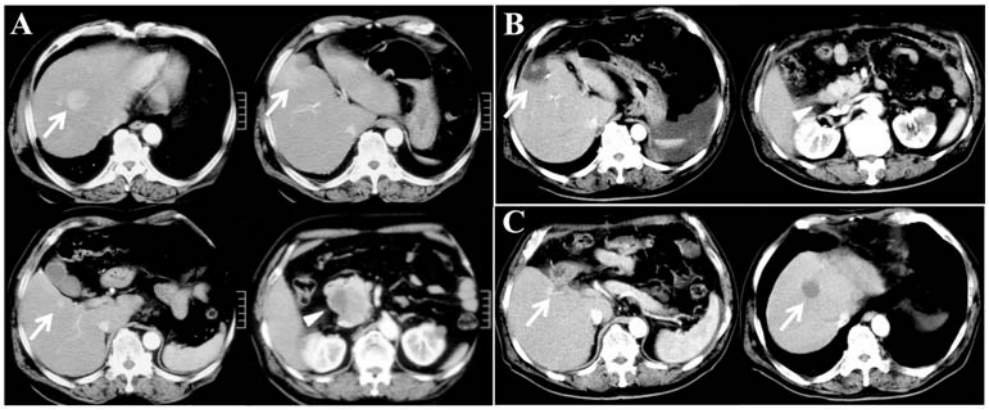

Figure 1.
The arterial phase images of abdominal dynamic contrast enhanced computed tomography (CT) of typical case of two-stage procedure for advanced HCC with LNM.
A) Before first treatment (hepatectomy and lymphoadenectomy), bilobar multiple intrahepatic HCC (arrows) and LNM in the pancreatic head area (arrow head) were detected as positive enhancement area. An extended right lobectomy was required for complete clearance of intrahepatic lesion. B) After second operation, postoperative change for partial hepatectomy (arrow) and lymphadencetomy (arrow head). C) After perctenous isolated hepatic perfusion (PIHP) as a locolegional treatment, residual intrahepatic lesions changed to low density areas indicating tumor necrosis.

Surgical procedure of lymphadenectomy

Surgical treatment for LNM was selective lymphadenectomy. A prophylactic lymph node dissection was not performed. The preoperative clinical diagnosis of LNM was based on the following findings from contrast-enhanced CT studies; (1) the short axis diameter of lymph node was minimally 10mm; (2) the lymph node showed hypervascularity in the

contrast-enhancement; (3) the size of lymph node became enlarged between following studies.

Statistical analysis

All data were analyzed using the statistical software JMP ver10 (SAS institute, cary, NC). The overall survival (OS) time was calculated from the date of lymphadenectomy. The mean value is shown as mean ± SE. The survival rates were calculated according to the Kaplan-Meier method. Differences in the survival curves were compared with log-rank statistics. *P* value less than 0.05 was considered as a statistically significant.

RESULTS

Table I lists the clinical characteristics of 15 patients with LNM. Twenty-seven nodes were pathologically proven as LNM from HCC. Hepatitis C virus was detected in 6 patients (40.0%) and 8 patients (53.3%) had cirrhotic liver. Among tumor factors, 10 patients (66.7%) had multiple HCCs. The vascular invasion was demonstrated in 9 patients (60.0%) in preoperative examination. The pathological features of HCC in 8 patients (53.3%) were

Table I. Demographics of 15 patients

Variable		Total	Group A	Group B	p
Host factor					
Age (year)	mean	63.1 ± 2.2	65.5 ± 2.3	60.3 ± 3.8	0.45
Sex	male/female	13/2	8/0	5/2	0.65
Viral hepatitis	none/HBs Ag/HCV Ab	6/3/6	2/2/4	4/1/2	0.44
Liver status	NL/CH/LC	3/4/8	1/3/4	2/1/4	0.57
Tumor factor					
Number of nodule	single/multiple	5/10	1/7	4/3	0.06
Maximum diameter (cm)	mean ± SE	5.3 ± 0.7	5.1	5.6	0.62
Gross classification †	SN/others	8/7	5/3	3/4	0.44
Vascular invasion	present/absent	9/6	4/4	5/2	0.39
TNM classification †	T2/T3/T4	5/4/6	2/3/3	3/1/3	0.55
Tumor cell differentiation †	mode/poor	7/8	5/3	2/5	0.18
Serum AFP (ng/ml)	≥ 10 / <10	12/3	6/2	6/1	0.6
Serum PIVKA II (mAU/ml)	≥ 40 / <40	11/4	6/2	5/2	0.87
LNM factor					
Time of appearance	synchronous/metachronous	6/9	4/4	2/5	0.39
Number per person	mean ± SE	1.8 ± 0.4	1.8 ± 0.5	2.0 ± 0.5	0.58
Diameter (cm)	mean ± SE	3.6 ± 1.8	3.5 ± 1.9	3.8 ± 1.5	0.32
Site	Hepatoduodenal ligament	8 (29.6%)	6	2	
	Common hepatic artery	8 (29.6%)	3	5	
	Retropancreatic head	5 (18.5%)	4	1	
	Para-aortic area	2 (7.4%)	0	2	
	Celiac axis	2 (7.4%)	1	1	
	Root of the mesentery	1 (3.7%)	1	0	
	Cervical area	1 (3.7%)	0	1	

Group A; With Residual Intrahepatic tumors after lymphadenectomy
Group B; Complete resection of both LNM and intrahepatic tumors

HCV, hepatitis C virus; HBV, hepatitis B virus; mode, moderately differentiated; poor, poorly differentiated;
AFP, alfa-feto protein; PIVKA II, protein induced by vitamin K absence or antagonist-II; SN, simple nodular type;
† According to The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, The 5th Edition, Revised Version from Liver Cancer Study Group of Japan.[41] And one patient had no pathological data for intrahepatic tumor.

either poorly differentiated type or undifferentiated type. The mean number of LNM was 1.8 ± 0.4, and the mean diameter was 3.6 ± 1.8 cm. Most common site of LNM was in the hepatoduodenal ligament and along the common hepatic artery (29.6%), followed by the posterior surface of pancreatic head area (18.5%). Six patients (40.0%) had synchronous LNM. In 9 patients with metachronous LNM, the mean time to detection of LNM after initial treatment for primary HCC was 13.7 ± 3.2 months. There is no significant difference between characteristic of patients in group A and B in term of host, tumor, and LNM factors.

Treatment courses of two groups were shown in **Table II**. There were no severe complications of lymphadenectomy. Five of 7 patients (71.4%) of Group B at initial presentation had eventually developed intrahepatic recurrence. Four patients (26.6%) of 15 patients developed lymph node recurrence. Patient No.12 had lymph node recurrence and died after the surgery that was performed for the cervical lymph node recurrence with superior vena cava tumor thrombosis. Patient No.13 died with gastric hemorrhage due to LNM invading to the stomach.

As of this writing, 6 of 15 patients (40.0%) are alive. The MST of 13 patients after lymph node resection was 25.2 months and the OS rates at 1, 2, and 3 years were 76.9%, 52.7%, and 26.4%, respectively. Kaplan-Meyer estimate indicated that the OS did not differ significantly between patients in group A and group B (*P*=0.78) (**Fig. 2**). In addition, neither host factors nor tumor factors associated statistically with OS rate. The number of LNM and lymph node recurrence after lymhadenectomy were not associated with prognosis. (**Table III**)

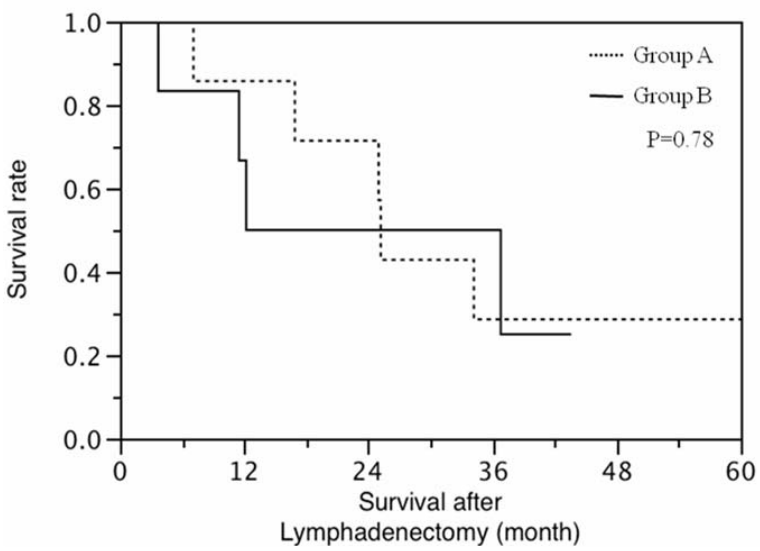

Figure 2.
Kaplan Meier estimate showed that there was no significant difference between OS rate of group A and group B (p=0.78).

Table II. Treatment courses of 15 patients after lymph node metastasis

Patient number	Age	Sex	Synchronous / Metachronous	Treatment before lymphadenectomy	Surgery with lymphadenectomy	Additional treatment	Site of recurrence	Survival after LNR (month)	Outcome
Group A (With Residual Intrahepatic tumors after lymphadenectomy)									
1	60	M	Metachronous	TACE	None	PIHP x2 TACE	Liver	25.0	Dead (IHTs)
2	63	M	Synchronous	None	Partial hepatectomy	PIHP x2 TACE	Liver	34.2	Dead (IHTs)
3	69	M	Metachronous	TACE Partial hepatectomy	S2 RFA	Partial hepatectomy RFA TACE	Liver	125.0	Alive
4	70	M	Metachronous	TACE Partial hepatectomy	None	PIHP x1	Liver	7.1	Dead IHTs)
5	56	M	Synchronous	None	Lt. hemihepatectomy	TACE sorafenib	Liver Rectum	25.2	Dead (IHTs)
6	61	M	Synchronous	None	None	PIHP x1 Lateral segmentectomy	Liver	43.1	Alive
7	77	M	Synchronous	None	Lt.hemihepatectomy	TACE RT	LN adrenal grand	16.9	Dead (Brain infarction)
8	68	M	Metachronous	Particle radio therapy	None	TACE	Liver	3.3	Alive
Group B (Complete resection of both LNM and intrahepatic tumors)									
9	72	M	Metachronous	TACE	Lt. hemihepatectomy	None	Liver	3.7	Dead (IHTs)
10	63	M	Metachronous	TACE RFA	Lateral segmentectomy	TACE	Liver	11.5	Dead (IHTs)
11	72	F	Synchronous	None	Rt hemehepatectomy	Lymphadenectomy	Liver LN	43.5	Alive
12	54	M	Metachronous	Lt. hemihepatectomy PIHP x2	None	Lung resection	LN Lung	12.2	Dead (Pulmonary embolism)
13	45	M	Metachronous	RFA	Partial hepatectomy	Lymphadenectomy	LN	36.8	Dead (Gastric hemorrhage due to LNM)
14	63	M	Synchronous	None	Lt.hemihepatectomy	TACE sorafenib	Liver	22.9	Alive
15	53	F	Metachronous	Partial hepatectomy	None	TACE	Liver	1.0	Alive

LN, lymph node; LNM, lymph node metastasis; IHTs, intrahepatic tumors; TACE, transcatheter arterial chemoembilization; PIHP, perctenous isolated hepatic perfusion; RFA, radiofrequency ablation;

Table III. Univariate analysis associated with overall survival

Variable	yes/no	MST (month)	*P*
Host factor			
Age (>65y)	6/9	16.9/25.2	0.92
Liver status (non LC or LC)	7/8	21.0/34.2	0.94
Tumor factor			
Larger than 5 cm in diameter	9/6	34.2/18.7	0.15
Multiple nodules	8/7	25.0/25.2	0.86
Vascular invasion	9/6	16.9/-	0.11
LNM factor			
Synchronous LNM	6/9	12.2/34.2	0.15
Solitary LNM	8/5	25.0/36.8	0.45
Lymph node recurrence	4/11	26.8/25.2	0.86

LNM, lymph node metastasis; LC, Liver cirrhosis; MST, median survival time;

DISCUSSION

An aggressive surgical treatment is oncologically contraindicated for malignant tumors with extensive LNM, because systemic spread of tumor cells is common. Also extended resection did not prolong survivals in the majority of patients in such circumstance (4, 18, 20, 32). Previous studies have shown that LNM of HCC is a poor prognostic factor and surgical resection of either intrahepatic tumors or LNM has not gained a wide clinical acceptance to date(23). On the other hand, however, several investigators have recently reported that long-term survival could be achieved after selective lymphadenectomy, when patients had a single LNM. In addition, these studies agreed that the success of locoregional treatment for intrahepatic tumors was a key element to prolong survivals in patients with LNM. Thus, it is reasonable to assume that selective lymphadenectomy could be a therapeutic option even for patients with multiple intrahepatic tumors for which a potent locoregional treatment could not be instituted.

We and others reported that the high efficacy of PIHP in the treatment of patients with multiple advanced HCC. In addition, PIHP, when combined with reductive hepatectomy for major intrahepatic tumors, it could exert even a stronger impact on multiple residual tumors in the liver. This hypothesis has been proven by the results of the dual treatment for patients with multiple advanced HCC which previously deemed to have a dismal prognosis. Of note, however, complete clearance of both intra- and extrahepatic tumors with surgical resection at a time is often difficult especially in patients with the cirrhotic liver. By this reason, 8 patients solely underwent selective lymphadenectomy at the first stage, and thereafter PIHP or other multimodal locoregional treatments such as TACE and RFA were done for intrahepatic residual tumors, depending on the number and distribution of hepatic tumors. As shown in Fig. 2, it is noteworthy that these 8 patients had an almost equivalent survival curve

to those without residual intrahepatic tumors at the time of lymphadenectomy. These results most likely support our treatment strategy for patients with multiple advanced HCC and LNM.

Although the number of patients in this pilot study was limited, we speculate that LNM from HCC was rather larger in size and smaller in number compared to other gastrointestinal malignant diseases. The mean diameter of LNM in this study was 3.6cm and nodes smaller than 2cm in diameter were detected in only three patients. On the other hand, the mean number of LNM per patient was 1.8 and five or more LNM were observed in only one patient. Of interest, gross finding of LNM was expansive in the majority of patients as was the dominant macroscopic finding of HCC in the liver. Such growth pattern of LNM from HCC may ease surgical resection in views of technical aspect.

Another to be considered is the mode of extrahepatic recurrence during the course. After selective lymphadenectomy, only 4 patients (26.7%) had eventually lymph node recurrence and two (13.3%) had distant metastasis other than LNM. This fact implies that LNM of HCC does not always indicate untreatable condition of the disease.

It is well known that the high rate of recurrence even after curative resection in the remnant liver is the most prominent feature of HCC. Our data have also shown that the local control of intrahepateic tumors was still a major obstacle to prolong survivals in patients with LNM. Indeed, intrahepateic recurrence was encountered in 13 of 15 patients. Six of 13 patients died after intrahepatic recurrence of HCC while death relating to LNM occurred in only two patients. Our data indicated that synchronous LNM was not statistically a poor prognostic factor. In addition, there was no significant difference between survivals of patients with synchronous and metachronous LNM. Other tumor and host factors did not differ between these two categories. Although the resectability of LNM was the greatest selection bias in our study, these observations strongly indicate that selective lymphadectomy can be justified in order to direct our treatment target to the intrahepateic tumors.

PIHP, TACE, and RFA are all locoregional treatment modalities, exerting their effects on only for intrahepatic tumors. In this regard surgical resection is the only realistic tool to eliminate LNM. Thus, we consider that the most effective therapeutic strategy for advanced HCC with LNM is the complete clearance of LNM combined with strategic locoregional treatments for intrahepatic tumors. Based on our experience, reductive surgery of major intrahepatic tumors and/or selective lymphadenectomy combined with PIHP represents one such treatment, and expands the therapeutic targets in patients with multiple intrahepatic tumors.

In conclusion, selective lymphadenectomy and aggressive multimodal and locoregional treatments for intrahepatic tumors, as represented by reductive hepatectomy followed by PIHP is the treatment of choice in selected HCC patients with multiple intrahepatic lesions and LNM.

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