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ORIGINAL ARTICLE

Oncologic Impact of Lymph Node Dissection for Intrahepatic Cholangiocarcinoma: a Propensity Score-Matched Study

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Abstract

Background Intrahepatic cholangiocarcinoma is a malignancy of the intrahepatic biliary tree. Although surgical resection is the mainstay of treatment for this tumor, the impact of lymph node dissection during hepatectomy is controversial. In this study, we evaluated the impact of lymph node dissection during surgical resection for intrahepatic cholangiocarcinoma.

Methods Records from 170 patients who underwent radical hepatectomy for intrahepatic cholangiocarcinoma from January 2000 to December 2014 were retrospectively reviewed. Twenty-two patients who underwent R1 resection or had distant metastasis at the time of surgery were excluded. Using propensity score matching (matched factors: differentiation, lymphovascular invasion, perineural invasion, and T stage), the patients were divided into two groups: no dissection ($n = 34$) or lymph node dissection ($n = 34$). Disease-free survival and overall survival were compared between groups.

Results There was a marginally significant difference between the two groups with respect to the disease-free survival (no dissection vs. lymph node dissection: 20.0 [4.2–35.8] months vs. 64.0 [27.3–120.8] months, $p = 0.077$). Overall survival was significantly longer in the lymph node dissection group (no dissection vs. lymph node dissection: 44.0 [31.1–56.9] months vs. 90.0 [51.1–158.9] months, $p = 0.027$).

Conclusion Radical surgery including an adequate lymph node dissection area and suitable harvested lymph nodes appears to improve oncologic outcomes for intrahepatic cholangiocarcinoma.

Keywords Intrahepatic cholangiocarcinoma · Hepatectomy · Lymph node excision · Treatment outcomes · Propensity score

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a malignancy of the intrahepatic biliary tree.[1] It is the second most common liver cancer after hepatocellular carcinoma and represents 10–15% of all primary liver cancers.[2] Recently, however, the incidence of ICC has increased progressively.[3] In the USA, the incidence of ICC increased almost threefold in the last 4 decades.[4] In accordance with this trend, there has been a growing interest in the management of ICC.

Surgical resection is the mainstay of treatment for ICC.[5] Numerous studies reported that surgical resection improves oncologic outcomes.[6,7] Some studies have demonstrated long-term survival of patients with ICC.[8] Most surgeons agree that surgical resection clearly has a positive impact in patients with ICC.

The impact of lymph node dissection (LND) during hepatectomy, however, is controversial. Although a substantial amount of research has examined this issue, no firm conclusions have been reached.[9,10] Indeed, no well-designed study, such as a randomized controlled trial, has been published regarding this issue, and current recommendations are primarily based on a consensus meeting of experts.[11]

The American Joint Committee on Cancer (AJCC) Cancer Staging System, 8th Edition, was recently published.[12] However, a study comparing the 8th and 7th editions found that the 8th edition did not improve prognostic ability during

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validation analysis, and the authors noted that one of the limitations of all staging systems is the relatively high number of patients who do not undergo lymphadenectomy.[13] Accordingly, there is a need to clarify the impact of LND for ICC.

In this study, we evaluated the oncologic impact of LND during surgical resection in patients with ICC to reflect the updated, 8th edition of the AJCC Cancer Staging System.[12,14]

Materials and Methods

Patient Characteristics

Data from 170 patients who underwent radical hepatectomy for ICC from January 2000 to December 2014 were retrospectively reviewed. Of these, 22 patients were excluded because they underwent R1 resection or had distant metastasis at the time of surgery. The remaining 148 patients were divided into three groups by LND status: no dissection, LN sampling, or LND.

LND was defined as harvesting more than six lymph nodes (LNs), including the removal of LNs around the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, along the common hepatic artery, and around the left gastric artery, regardless of tumor location. This definition was based on the number of LNs recommended by the AJCC Cancer Staging System, 8th Edition.[12] LN sampling was defined as LN removal that did not meet the criteria for LND.

Assessment of LND Impact Using Propensity Score Matching

Propensity score matching was performed with the no dissection and LND groups, resulting in 34 patients in each matched group. Differentiation, lymphovascular invasion (LVI), perineural invasion (PNI), and T stage were chosen as matched factors, and the sample ratio was 1:1. Disease-free survival (DFS) and overall survival (OS) were compared between the no dissection and LND groups (Fig. 1).

Statistics

IBM SPSS Statistics version 21.0 (IBM Corp., Somers, NY) and R version 2.14.2 were used for all statistical analyses. We compared nominal data using χ^2 tests, continuous parametric data using t tests, and non-parametric data using Mann-Whitney tests. Survival parameters were assessed by the Kaplan-Meier method and compared using the log-rank test. The criterion for statistical significance was a p value < 0.05.

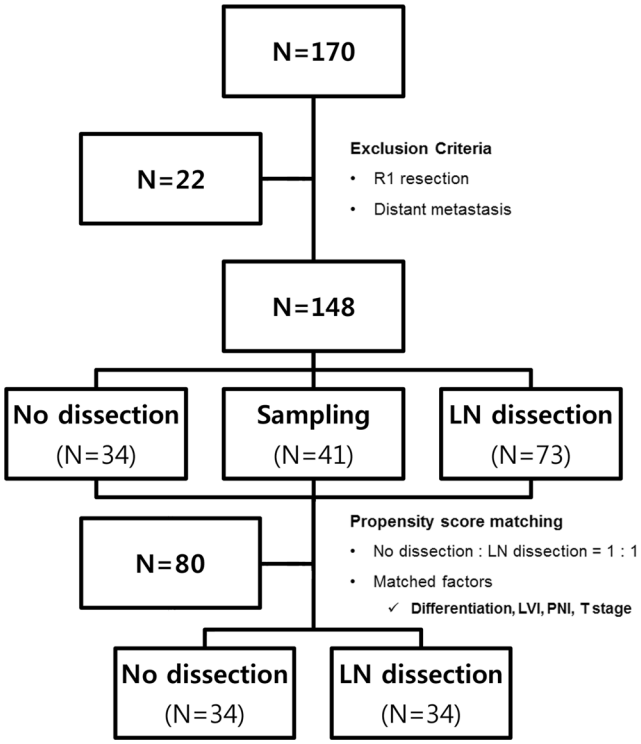

Fig. 1 Flow chart of the patient selection and group assignment processes. LN lymph node, LVI lymphovascular invasion, PNI perineural invasion

Results

Clinicopathologic Characteristics

Clinicopathologic characteristics of the 148 patients are shown in Table 1. Their mean age was 63 ± 10.2 years. The no dissection group included 34 patients (23.0%), the LN sampling group included 41 patients (27.7%), and the LND group included 73 patients (49.3%). In the LN sampling and LND groups, LN metastases were noted during pathologic examination in 42 patients (36.8%). The ICC was mainly located on the left side of the liver in 81 patients (54.7%) and on the right side in the other 67 patients (45.3%). Median follow-up duration was 65.0 [55.3–74.7] months.

Characteristics According to Lymph Node Dissection Status

The median number of harvested LNs was 12 [8–18] in the LND group and 3 [1–4] in the LN sampling group. Operation type (major vs. minor; $p = 0.001$), tumor size ($p = 0.016$), LVI ($p = 0.034$), PNI ($p = 0.011$), T stage ($p = 0.031$), N stage ($p < 0.001$), and adjuvant therapy ($p = 0.004$) exhibited significant differences among the three groups (Table 2).

Table 1 Clinicopathologic characteristics of 148 patients with intrahepatic cholangiocarcinoma

Characteristic	Value
Age (years)	63.2 ± 10.2
Gender (male:female)	92:56 (1.6:1)
Hepatitis (B or C viral carrier)	28 (15.6%)
IHD stone	9 (6.1%)
CA 19-9	31.8 [8.1–232.0]
Neoadjuvant therapy	14 (9.5%)
Operation type	
Major (≥ 3 segments)	126 (85.1%)
Minor (< 3 segments)	22 (14.9%)
LN dissection management	
No dissection	34 (23.0%)
Sampling	41 (27.7%)
LN dissection	73 (49.3%)
Tumor location (left:right)	81:67 (1.2:1)
Tumor size (cm)	4.6 ± 2.4
Tumor number	
Single	127 (85.8%)
Multiple	21 (14.2%)
Gross type	
IG	21 (14.2%)
PI	9 (6.1%)
MF	97 (65.5%)
Mixed	21 (14.2%)
Differentiation[a]	
Well	26 (17.6%)
Moderately	68 (45.9%)
Poorly	44 (29.7%)
Undifferentiated	5 (3.4%)
LVI	89 (60.1%)
PNI	50 (33.8%)
Number of harvested LNs[b]	5 [1–12]
T stage	
T1	23 (15.5%)
T2	81 (54.7%)
T3	41 (27.7%)
T4	3 (2.0%)
N stage	
N0	72 (48.6%)
N1	42 (28.4%)
Nx	34 (23.0%)
TNM stage	
I	22 (14.9%)
II	55 (37.2%)
III	28 (18.9%)
IV	43 (29.1%)
Adjuvant therapy	58 (39.2%)
Median follow-up (months)	65.0 [55.3–74.7]

[a] Data available for only 143 patients

[b] For patients in the lymph node sampling and lymph node dissection groups

IHD, intrahepatic duct; *CA*, carbohydrate antigen; *LN*, lymph node; *IG*, internal growth; *PI*, periductal infiltrate; *MF*, mass forming; *LVI*, lymphovascular invasion; *PNI*, perineural invasion

Characteristics After Propensity Score Matching

Propensity score matching was performed between the no dissection group and LND group. After matching, there were no significant differences between the no dissection and LND groups, except the operation type (no dissection vs. LND: major operation 64.7% vs. 88.2%, $p = 0.043$) (Table 3).

Survival Outcomes According to LN Management

There was a marginally significant difference between the two groups with respect to the disease-free survival (no dissection vs. LND: 20.0 [4.2–35.8] months vs. 64.0 [27.3–120.8] months, $p = 0.077$) (Fig. 2a). OS was significantly longer in the LND group than in the no dissection group (no dissection vs. LN dissection: 44.0 [31.1–56.9] months vs. 90.0 [51.1–158.9] months, $p = 0.027$) (Fig. 2b).

Discussion

Many previous studies have reported prognostic factors after radical surgery for ICC, including tumor size, multiple lesions, cirrhosis, differentiation, LVI, PNI, and tumor markers.[15,5,16–20] LN metastasis has also been identified as a major prognostic factor after radical surgery for ICC;[21,22] however, the role of routine lymphadenectomy remains controversial.[23] Some authors advocated routine lymphadenectomy, whereas others did not. Interestingly, most eastern studies tended to recommend lymphadenectomy, whereas western studies did not.[9]

One reason cited against routine lymphadenectomy for ICC was the lack of improved outcomes with LND compared to no dissection in some studies.[24,25] Other authors regarded ICC with LN metastasis as a systemic disorder, which is difficult to control with surgery alone.[26] Furthermore, lymphadenectomy increases the risk of certain complications, such as vascular injury.[27]

However, this opinion has a fundamental error, because the dissected area of LN was not defined in each article.[14,24,25,27–32] This point applies equally to the counterpart who advocate routine lymphadenectomy. The area of LND usually depended on the general policy of the institute or surgeon. Accumulating knowledge regarding lymph flow of the liver has gradually led to the establishment of optimal areas of LND.[33–35] In particular, knowing that lymphatic drainage can differ according to the tumor's location, most surgeons who advocated LND performed at least regional dissection.[36,35,37] In our study, the surgeon who advocated LND performed this and the study results showed that OS of patients was significantly longer in the LND group than in the no dissection group.

The report of the expert consensus meeting indicated that the ideal lymphadenectomy included all regional nodal stations and recommended routine removal of these stations.[11] As a result, radical surgery with LND, including the removal of LNs around the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, and along the common

Table 2 Characteristics according to lymph node dissection status

Characteristic	No dissection ($n = 34$)	LN sampling ($n = 41$)	LN dissection ($n = 73$)	p value
Age (years)	64.5 ± 9.1	62.5 ± 9.6	62.9 ± 8.3	0.664
Gender (male:female)	17:17 (1.0:1)	26:15 (1.7:1)	49:24 (2.0:1)	0.240
Hepatitis (viral carrier)	6 (17.6%)	9 (22.0%)	7 (9.6%)	0.171
IHD stone	4 (11.8%)	2 (4.9%)	3 (4.1%)	0.348
CA 19-9	42.0 [4.2–235.5]	58.7 [7.4–226.5]	23.6 [11.1–261.5]	0.823
Neoadjuvant therapy	3 (8.8%)	7 (17.1%)	4 (5.5%)	0.116
Operation type				0.001
Major (≥ 3 segments)	22 (64.7%)	36 (87.8%)	68 (93.2%)	
Minor (< 3 segments)	12 (35.3%)	5 (12.2%)	5 (6.8%)	
Tumor location (left:right)	21:13 (1.6:1)	19:22 (0.9:1)	42:31 (1.3:1)	0.390
Tumor size (cm)	3.7 ± 2.2	4.5 ± 2.5	5.1 ± 2.2	0.016
Tumor number				0.483
Single	27 (79.4%)	36 (87.8%)	64 (87.7%)	
Multiple	7 (20.6%)	5 (12.2%)	9 (12.3%)	
Gross type				0.492
IG	4 (11.8%)	7 (17.1%)	10 (13.7%)	
PI	21 (61.8%)	30 (73.2%)	46 (63.0%)	
MF	3 (8.8%)	2 (4.9%)	4 (5.5%)	
Mixed	6 (17.6%)	2 (4.9%)	13 (17.8%)	
Differentiation[a]				0.205
Well	10 (29.4%)	7 (18.4%)	9 (12.7%)	
Moderately	16 (47.1%)	20 (52.6%)	32 (45.1%)	
Poorly	8 (23.5%)	10 (26.3%)	26 (36.6%)	
Undifferentiated	0 (0.0%)	1 (2.6%)	4 (5.6%)	
LVI	15 (44.1%)	23 (56.1%)	51 (69.9%)	0.034
PNI	5 (14.7%)	13 (31.7%)	32 (43.8%)	0.011
Number of harvested LNs	0 [0–0]	3 [1–4]	12 [8–18]	< 0.001
T stage				0.031
T1	8 (23.5%)	8 (19.5%)	7 (9.6%)	
T2	23 (67.7%)	19 (46.3%)	39 (51.4%)	
T3	3 (8.8%)	13 (31.7%)	25 (34.2%)	
T4	0 (0.0%)	1 (2.4%)	2 (2.7%)	
N stage				< 0.001
N0	0 (0.0%)	31 (75.6%)	41 (56.2%)	
N1	0 (0.0%)	10 (24.4%)	32 (43.8%)	
Nx	34 (100.0%)	0 (0.0%)	0 (0.0%)	
Adjuvant therapy	7 (20.6%)	13 (31.7%)	38 (52.1%)	0.004

*Data available for only 143 patients

IHD, intrahepatic duct; *CA*, carbohydrate antigen; *LN*, lymph node; *IG*, internal growth; *PI*, periductal infiltrate; *MF*, mass forming; *LVI*, lymphovascular invasion; *PNI*, perineural invasion

Table 3 Patient characteristics after propensity score matching

Characteristic	No dissection ($n = 34$)	LN dissection ($n = 34$)	p value
Age (years)	64.5 ± 9.1	63.1 ± 9.1	0.533
Gender (male:female)	17:17 (1.0:1)	21:13 (1.6:1)	0.464
Hepatitis (viral carrier)	6 (17.6%)	4 (11.8%)	0.734
IHD stone	4 (11.8%)	3 (8.8%)	> 0.999
CA 19-9	42.0 [4.2–235.5]	19.1 [6.8–74.4]	0.602
Neoadjuvant therapy	3 (8.8%)	1 (2.9%)	0.614
Operation type			0.043
Major (≥ 3 segments)	22 (64.7%)	30 (88.2%)	
Minor (< 3 segments)	12 (35.3%)	4 (11.8%)	
Tumor location (left:right)	21:13 (1.6:1)	18:16 (1.1:1)	0.624
Tumor size (cm)	3.7 ± 2.2	4.8 ± 2.7	0.070
Tumor number			0.054
Single	27 (79.4%)	33 (97.1%)	
Multiple	7 (20.6%)	1 (2.9%)	
Gross type			0.228
IG	4 (11.8%)	10 (29.4%)	
PI	21 (61.8%)	20 (58.8%)	
MF	3 (8.8%)	1 (2.9%)	
Mixed	6 (17.6%)	3 (8.8%)	
Differentiation			1.000
Well	10 (29.4%)	10 (29.4%)	
Moderately	16 (47.1%)	16 (47.1%)	
Poorly	8 (23.5%)	8 (23.5%)	
Undifferentiated	0 (0.0%)	0 (0.0%)	
LVI	15 (44.1%)	16 (47.1%)	> 0.999
PNI	5 (14.7%)	5 (14.7%)	1.000
Number of harvested LNs	0 [0–0]	10 [8–18]	< 0.001
T stage			0.809
T1	8 (23.5%)	8 (23.5%)	
T2	23 (67.7%)	19 (56.0%)	
T3	3 (8.8%)	6 (17.6%)	
T4	0 (0.0%)	1 (2.9%)	
N stage			< 0.001
N0	0 (0.0%)	22 (64.7%)	
N1	0 (0.0%)	12 (35.3%)	
Nx	34 (100.0%)	0 (0.0%)	
Adjuvant therapy	7 (20.6%)	11 (32.4%)	0.410
Major Cx[a]	3 (8.8%)	4 (11.8%)	> 0.999

[a] Complications with a Clavien-Dindo classification ≥IIIA

IHD, intrahepatic duct; *CA*, carbohydrate antigen; *LN*, lymph node; *IG*, internal growth; *PI*, periductal infiltrate; *MF*, mass forming; *LVI*, lymphovascular invasion; *PNI*, perineural invasion; *Cx*, complication

hepatic artery, is an accepted treatment for ICC. Moreover, if the tumor is located on the left side of the liver, LN around the left gastric artery is also included in the LND. These recommendations were reflected in the AJCC Cancer Staging System, 8th Edition. In addition, for complete pathological

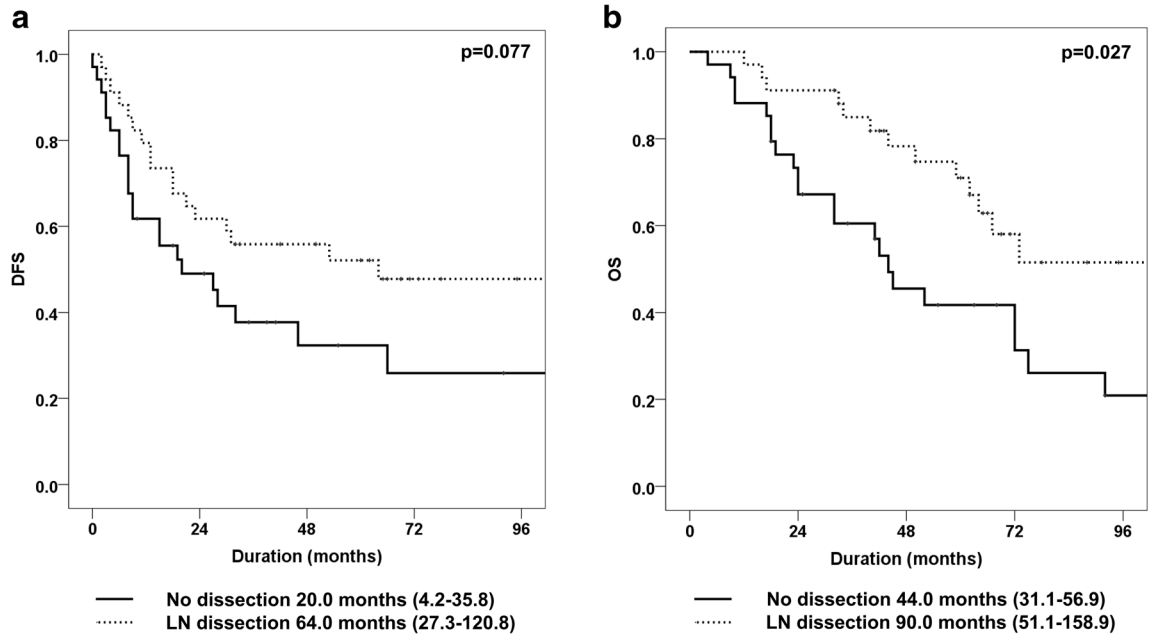

Fig. 2 Survival rates according to lymph node dissection status. **a** Disease-free survival and **b** overall survival. DFS disease-free survival, OS overall survival, LN lymph node

staging, harvesting of at least six lymph nodes from appropriate nodal stations is recommended.[12]

Before the consensus meeting, most studies did not describe the exact area of LND,[29,31] and the few that described the area did not provide information about the LNs that were harvested.[27,24,25] Studies published after the consensus meeting also did not describe the exact area of LND.[30,32]

Previously, our institution published an article about the impact of LND for ICC. At that time, we reported that regional + α lymph node dissection enhanced survival in patients with ICC.[14] For this study, we reviewed data from previous and additional patients and reclassified LND according to the AJCC Cancer Staging System, 8th Edition.

A unique aspect of the current study is that LND was performed around the left gastric artery regardless of the tumor's location. Reviewing the data, tumors from 6 patients (9.4%) extended across lobar boundaries to involve both the left and right lobes. Three of these tumors were mainly located in segment 4, whereas the other 2 were mainly located in segment 5. Moreover, the tumor in 1 patient was mainly located in the caudate lobe. Because there is no consensus regarding the preferred area of LND in these situations, LND included the left gastric artery area in all patients, regardless of their tumor location to evaluate the pure impact of LND for ICC.

Reviewing previous studies, most LNDs appeared to be performed for advanced disease, including extremely large tumors, tumors with vascular invasion, and multinodular tumors.[14,27,32] This may have introduced selection bias and masked the impact of LND. To reduce the possibility of this error, we analyzed the data after propensity score matching. By matching known prognostic factors for ICC, we attempted to minimize differences between groups. As a result, our study showed a positive impact of LND during surgery for ICC.

In the current study, we also showed that LND did not increase the rate of major complications after radical surgery for ICC, compared with no LND (Table 3). No vascular complications, such as aneurysm or rupture, occurred in the LND group. Although 1 patient in the LND group developed chyle leakage, this resolved with conservative care. It is regarded that the risks have decreased due to advanced medical and surgical technique and the risks do not increase due to LND.

Although this study found that radical resection with LND for ICC may improve oncologic outcomes, it has some limitations. The study's design was a retrospective review. We used propensity score matching to reduce the risk of bias, but a well-designed prospective study or a randomized controlled trial is necessary to provide more definitive conclusions about the impact of LND. Another limitation involved the no dissection group. Although propensity score matching was used to control for prognostic factors as much as possible, this group was heterogenous, and it was difficult to determine whether they had metastatic or non-metastatic LNs. Preoperative image studies may have provided more information regarding the nature of these nodes.[38] Another study limitation was that we did not evaluate the impact of LN sampling. Further study will be necessary to evaluate this issue.[33]

Conclusion

When controlling for other prognostic factors by propensity score matching, this study showed that LND, which is recommended by updated guidelines for ICC management, impacted outcomes. Radical surgery including an adequate LN dissection area and suitable harvested LNs appeared to improve oncologic outcomes for ICC. Further, well-designed prospective studies are required to more fully address this issue.

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Analysis and interpretation of data
Drafting the article
Dae Hoon Han: Acquisition of data
Gi Hong Choi: Acquisition of data
Jin Sub Choi: Acquisition of data
Kyung Sik Kim: Contribution to conception and acquisition of data
Final approval of the version to be submitted and any revised version

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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