Role of posterosuperior pancreatic lymph nodes in gallbladder cancer: A study using the efficacy index

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Abstract. Gallbladder cancer (GBC) is an aggressive malignancy with a poor prognosis, for which radical surgery, including lymph node (LN) dissection, remains the only potentially curative treatment. However, the optimal extent of LN dissection has yet to be sufficiently established. The present study sought to evaluate different LN dissection strategies by analyzing the patterns of LN metastasis and calculating the lymph node dissection efficacy index (EI) for each nodal station. A retrospective analysis was conducted on 42 patients with GBC who underwent gallbladder bed resection or more extensive procedures with LN dissection. The prognostic outcome of each LN dissection was assessed using the EI. LN metastases and recurrence were identified in 12 and 14 patients, respectively. Among the four patients with negative metastasis in the hepatoduodenal ligament (LN#12) and positive metastasis in the posterosuperior pancreatic LN (LN#13a), one case remained recurrence-free. Compared with LN along the common hepatic artery (LN#8, 2.94) and LN#12 (4.76), the highest EI value (5.88) was obtained for LN#13a, thereby highlighting its utility in surgical management. Overall, LN#13a might be considered regional nodes for GBC, and should accordingly be dissected, and even in cases in which intraoperative sampling reveals no metastasis in LN#12, dissection of LN#13a warrants consideration.

Introduction

Gallbladder cancer (GBC) is an aggressive malignancy with a poor prognosis, and radical surgery remains the only potentially curative treatment (1). Lymph node (LN) metastasis has been reported in 40 to 50% of T2 GBC and in ≥60% of T3 cases (2-5). LN metastasis is strongly associated with an increased risk of recurrence, underscoring the critical role of LN dissection in therapeutic strategies.

The standard surgical procedure for GBC typically involves liver resection with lymphadenectomy, targeting areas determined by lymphatic drainage from the primary tumor. However, the optimal extent of LN dissection remains a matter of debate among international guidelines, including those established by the American Joint Committee on Cancer (AJCC) (6), the Union for International Cancer Control (UICC) (7) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) (8). Notably, the Japanese guidelines uniquely recommend dissection of the posterosuperior pancreatic LNs (PSPLNs; LN#13a).

Although several studies have evaluated LN dissection for GBC, the therapeutic value of each nodal station remains unclear, and further evidence is required to guide surgical decisions (1,9,10). Clarifying the clinical significance of specific nodal basins is essential for optimizing the balance between radicality and invasiveness in surgical management.

The present study aimed to determine the optimal extent of LN dissection based on the sites of LN metastasis and to assess the impact of LN dissection by calculating the LN dissection efficacy index (EI) in patients with GBC who underwent gallbladder bed resection or more extensive procedures with LN dissection.

Materials and methods

Study design and participants. The present study retrospectively collected and analyzed the clinicopathological data of 42 patients who underwent curative surgery for GBC at Nishi-Kobe Medical Center (Kobe, Japan) between January 2000 and January 2021. Eligible cases included patients with suspected GBC preoperatively or those in whom GBC was confirmed through pathological examination following cholecystectomy for cholelithiasis or cholecystitis, followed by a second radical surgery. LN dissection was defined as the systematic dissection of at least the LNs of the hepatoduodenal ligament (LN#12), and patients who underwent only LN sampling were excluded. Patients who did not undergo liver resection or LN dissection, as well as

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Abbreviations: GBC, gallbladder cancer; LN, lymph node; EI, efficacy index; PSPLN, posterosuperior pancreatic lymph node

Key words: gallbladder cancer, lymph node dissection, posterosuperior pancreatic lymph node, efficacy index, optimal extent of lymph node dissection

those diagnosed with benign disease on pathological examination, were excluded from the study. These patients were excluded because whole-layer cholecystectomy or limited LN sampling does not allow for accurate calculation of the EI (11), and omission of hepatic resection may not meet the criteria for standard oncological resection in GBC, potentially confounding the analysis (12,13). In total, 10 patients were excluded based on these criteria. This study was approved by the Ethics Committee of the Nishi-Kobe Medical Center (approval no. 2024-60).

Data collection and definitions. Patient demographic information, operative details, pathological tumor and LN characteristics, and survival outcomes were collected from medical records. Systematic LN dissection was confirmed using surgical records, intraoperative photographs and video recordings. The 8th edition of the UICC TNM classification was used to evaluate clinical outcomes (7). However, owing to the lack of a clear distinction between T2a and T2b in a number of older cases, these classifications were not differentiated in the present study. Postoperative complications were categorized using the Clavien-Dindo classification system (14).

Intraoperative frozen section analysis of LN#12 was not performed in any case. The extent of lymph node dissection was determined preoperatively based on the estimated tumor invasion depth and the general condition of the patient, following the institutional surgical strategy for gallbladder cancer. LN#13a dissection was generally planned when invasion beyond the subserosal layer (≥T2) was suspected and the operative risk was acceptable, whereas LN#12 dissection alone was selected in cases with higher operative risk or limited resectability.

The anatomical boundaries of the LN stations were defined according to the guidelines of the JSHBPS (13). LN#8 was defined as nodes along the common hepatic artery, LN#12 as nodes along the hepatoduodenal ligament, and LN#13a as nodes along the superior border of the pancreatic head.

Continuous variables are presented as median (range), and categorical variables are expressed as counts.

Lymph node dissection EI. The relationship between LN metastasis at each station and prognosis was assessed using the EI proposed by Sasako *et al* (11). The EI was calculated as the product of the frequency of metastasis at a given station and the 3-year survival rate. Specifically, the EI was calculated using the following formula: EI=[frequency of metastasis at the station (%)] x [3-year survival rate among patients with metastasis at that station (%)]/100.

While Sasako *et al* (11) originally used the 5-year survival rate, the present study employed the 3-year rate because of the generally poor prognosis associated with GBC.

Due to the small sample size and limited number of nodal metastases, no statistical tests were performed to compare the EIs between nodal stations, as such analyses would have lacked robustness.

Results

Patient characteristics and perioperative parameters. The clinical characteristics of the 42 patients included in the study are summarized in Table I. The median age was 72 years (range, 45-87 years), and 24 patients were male. Among all patients, 22 underwent gallbladder bed resection, including S4a + S5 resections, seven of whom underwent a second surgery following a prior cholecystectomy in which GBC was diagnosed. Among all 42 patients, 16 underwent gallbladder bed resection with bile duct resection, and four patients underwent more extensive liver resection beyond hepatic lobectomy.

Table I. Summary of characteristics of patients.

Characteristic	Value
Median age (range), years	72 (45-87)
Male/female sex, n	24/18
Procedure, n	
Gallbladder bed resection (including S4a + S5)	22
Gallbladder bed resection + bile duct resection	16
Liver resection beyond hepatic lobectomy	4
Median operation time (range), min	288 (113-653)
Median blood loss (range), g	268 (33-1,320)
Transfusion (+/-), n	5/37
Median harvested lymph nodes (range), n	7.5 (1-26)
Clavien-Dindo ≥ grade 2, n	15
Cholangitis	6
Abscess/fluid collection	4
Bile leakage	3
Pulmonary embolism	1
Wound infection	1
Median hospital stay (range), days	13 (6-101)

The median operative time was 288 min (range, 113-653 min), and the median intraoperative blood loss was 268 ml (range, 33-1,320 ml). Blood transfusions were required in five patients. The median postoperative hospital stay was 13 days (range, 6-101 days).

Pathological data and oncological outcome. The pathological findings, including tumor depth, LN metastasis and recurrence, are presented in Table II. Tumor depth was classified as T1a in three patients, T1b in five, T2 in 25, T3 in nine, and T4 in none. Pathological LN metastases were detected in 12 patients, of whom nine experienced recurrence. Recurrence was observed in 14 patients overall.

Site of lymph node metastasis and recurrence. The distributions of LN metastases and associated recurrences are summarized in Table III. Metastases confined to LN#12 were observed in four patients, all of whom experienced recurrence. Among the four patients with metastases limited to LN#13a, one remained recurrence-free. In one patient with metastases involving both LN#12 and LN#13a, and another patient with metastases involving LNs along the common hepatic artery (LN#8) and LN#12 no recurrence was observed. Conversely,

Table II. Tumor depth, lymph node metastasis and recurrence.

Tumor depth	LN metastasis		Recurrence	Site of recurrence				
				Local	Dissemination	Para-aorta LN	Distance	Distance and local
T1a	+	0	0	-	-	-	-	-
	-	3	0	-	-	-	-	-
T1b	+	0	0	-	-	-	-	-
	-	5	1	-	-	-	-	1
T2	+	5	3	-	1	1	1	-
	-	20	4	1	1	1	1	-
T3	+	7	6	-	1	2	3	-
	-	2	0	-	-	-	-	-

LN, lymph node.

Table III. Lymph node metastases and recurrence.

Lymph node metastasis	Value (n=12)	Recurrence
#12 only	4	4
#13a only	4	3
#12 and #13a	1	0
#8 and #12	1	0
#12 and #16	1	1
#8, #12, #13a and #16	1	1

Table IV. Efficacy index of each lymph node.

LN	Dissection (n)	Metastasis (n)	3 years survival rate (%)	Efficacy index
#8	34	2	50.0	2.94
#12	42	8	25.0	4.76
#13a	34	6	33.3	5.88

LN, lymph node.

both patients with LN#16 metastases (resected by sampling) experienced recurrence.

EI assessment for each nodal station. The EI values for each LN station are presented in Table IV. The calculated EI was 4.76 for LN#12, 2.94 for LN#8, and 5.88 for LN#13a.

Discussion

In GBC, the depth of tumor invasion is a critical factor in determining treatment strategies. However, the accuracy of preoperative diagnosis of tumor depth remains limited, with reported rates as low as 55% (15). Furthermore, the sensitivity and specificity of preoperative detection of LN metastasis vary widely, ranging from 25 to 93% (16-18) and 74 to 90% (16,19,20), respectively. Because of the challenges in accurately diagnosing LN metastasis preoperatively and the high likelihood of LN involvement in tumors invading deeper than T2, LN dissection should be included in the surgical approach when tumor invasion beyond T2 is suspected. Although cholecystectomy with liver resection and lymphadenectomy are standard procedures in such cases, the optimal extent of LN dissection remains controversial.

Kishi *et al* (9) reported that even with metastasis to the peripancreatic LN, the 5-year survival rate was 34%, which is almost equivalent to the 36% survival rate for metastasis to the LNs along the hepatoduodenal ligament and common hepatic artery, highlighting the significance of PSPLN dissection. However, the efficacy of dissection at specific LN stations, such as LN#8, LN#12 and LN#13a, remains unclear. To address this

issue, the present study specifically evaluated the effectiveness of LN dissection at each station using the EI.

Our results demonstrated that the EIs for LN#8 (2.94) and LN#13a (5.88) were comparable to those EIs for regional LNs in gastric cancer, such as LN#5 (2.7) and LN#8 (5.9) (11). These findings support the inclusion of LN#8, #12 and #13a as regional LNs in GBC. Additionally, the calculated EI for LN#13a (5.88) was higher than that for LN#12 (4.76) and LN#8 (2.94), suggesting a comparable or even greater survival benefit. These findings, together with previous reports (9,10,21), reinforce the recommendation of the Japanese guidelines to include LN#13a as a regional lymph node in GBC.

In the present study, four patients with negative LN#12 and positive LN#13a findings included one case without recurrence. This suggests that LN#13a dissection may be considered even when LN#12 is negative on rapid intraoperative pathological examination. However, given the limited sample size and the retrospective nature of the present study, this recommendation should be interpreted cautiously and validated in larger cohorts. Supporting this, a previous report indicated the possibility of metastasis to other regional LNs despite negative LN#12 findings (10). Kokudo *et al* (10) emphasized the importance of LN#13a dissection and noted that positive LN#13a findings were associated with metastases to the common hepatic artery nodes and to those in front of the pancreatic head. Similarly, Higuchi *et al* (21) reported a 5-year survival rate of 91.7% in patients with T2 GBC and LN#13a metastasis. These studies support the utility of LN#13a dissection. The apparent significance of LN#13a compared with other stations may be explained by its anatomical location along the drainage pathway from the gallbladder via the cystic duct and common bile duct to the pancreaticoduodenal nodes. However, this hypothesis requires further investigation.

The present study had several limitations. First, it was conducted at a single institution with a small sample size, which limited the statistical power for comparing the EI among nodal stations. Because of the small sample size, no multivariate analyses such as Cox regression could be performed. Consequently, the potential confounding effects of covariates on survival outcomes cannot be excluded. Nevertheless, demonstrating the potential efficacy of LN#13a dissection using the EI is an important finding. Second, as no patients undergoing pancreatoduodenectomy were included, the significance of performing pancreatoduodenectomy for LN#13a dissection could not be evaluated. Third, 10 patients were excluded, including those who underwent whole-layer cholecystectomy and those who received only LN sampling instead of sufficient dissection. These exclusions may have influenced EI. Fourth, no patients in this cohort underwent LN#14 or LN#9 dissection, and, therefore, the efficacy of LN dissection at these stations could not be evaluated. However, based on previous studies, the clinical significance of the dissection of LN#14 and LN#9 in GBC is presumed to be lower than that of LN#13 (3,4,9,21-23). The roles of other nodal stations, such as LN#9 and LN#14, should be further evaluated to clarify their clinical significance. Finally, our cohort included patients who underwent different extents of resection, such as gallbladder bed resection, bile duct resection, extended hepatectomy and radical second surgery. These variations in surgical procedures may have influenced the number of retrieved LNs and the risk of recurrence. Therefore, the effect of surgical procedure heterogeneity cannot be excluded, and our findings should be interpreted with caution. However, due to the limited sample size, the present study was unable to perform stratified analyses or statistical adjustments according to the type of surgery, which may have affected the interpretation of the results.

In conclusion, the present study provides evidence supporting the classification of PSPLNs as regional nodes in GBC and emphasizes the necessity of dissection in surgical management. Even when LN#12 metastasis was negative during intraoperative sampling, LN#8 and #13a dissection might still be considered. However, this finding should be interpreted with caution, given the limited sample size, and further validation in larger, multi-institutional studies is required.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KY and TH performed the conception and design of the study. KY, SN, HT and TH performed the analysis and interpretation of data. KY, SN, HT, SY, HF, TH, TK and AI performed the collection and assembly of data. KY drafted of the article. KY and TH confirm the authenticity of all the raw data. All authors participate in critical revision of article for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nishi-Kobe Medical Center (approval no. 2024-60), was conducted in accordance with the principles of the Declaration of Helsinki, and written consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors

revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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