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Extended Lymphadenectomy Is Required for Incidental Gallbladder Cancer Independent of Cystic Duct Lymph Node Status

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Abstract

Background We examined whether the incidental cystic duct nodal status predicts the status of the hepatoduodenal ligament (D1) or common hepatic artery, the pancreaticoduodenal and paraaortic lymph nodes (D2), and the overall prognosis and thus indicates whether an oncologic extended resection (OER) is required.

Methods The study included patients who underwent OER for incidental gallbladder cancer (IGBC) during 1999–2015. Associations between a positive cystic duct node and D2 nodal status and disease-specific survival (DSS) were analyzed.

Results One-hundred-eight-seven patients were included. Seventy-three patients (39%) had the incidental cystic duct node retrieved. Cystic duct node positivity was associated with positive D1 (odds ratio 5.2, $p = 0.012$) but not with D2. Among all patients, a positive cystic duct node was associated with worse DSS (hazard ratio [HR] 2.09). Patients without residual cancer at OER and positive incidental cystic duct node had similar DSS to patients with negative nodes 70 vs 60% ($p = 0.337$). Positive D1 (HR 6.07) or positive D2 (HR 13.8) was predictive of worse DSS.

Conclusions Patients with no residual cancer at OER and regional disease limited to their incidental cystic duct node have similar DSS to pN0 patients. The status of the cystic duct node only predicts the status of hepatic pedicle nodes.

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Keywords Gallbladder neoplasm · Gallbladder cancer · Lymphadenectomy · Lymph node dissection · Prognostication · Survival

Introduction

Gallbladder cancer is the most common biliary tract malignancy worldwide.[1] The 5-year survival rate for patients with advanced gallbladder cancer is less than 5%.[2] However, when the disease is discovered in its early stages, the 5-year survival rate can approach 75%.[3] Complete oncologic extended resection (OER) comprises a limited resection of the liver bed, anatomic resection of liver segments 4b and 5, or, rarely, major liver resection (≥3 Couinaud's segments) associated to regional lymphadenectomy including the hepatoduodenal ligament, hepatic artery, and retropancreatic lymph node stations. OER remains the only effective and potentially curative therapy for gallbladder cancer.[4,5]

Incidental gallbladder cancer (IGBC) is the most common form of gallbladder cancer diagnosed today.[6] In patients with IGBC, decisions regarding the need for re-resection and neoadjuvant therapy before re-resection are based on histopathologic analysis of the index cholecystectomy specimen. Several factors have been considered in order to select the proper treatment, including T category, presence of perineural or lymphovascular invasion, status of the liver bed margin, presence of disease in the cystic duct stump, and the presence of metastasis in the cystic duct lymph node. Results from our recent study suggested that residual cancer could be a criterion for consideration of neoadjuvant therapy before re-resection in patients with IGBC.[7]

The cystic duct node, also referred to as Calot's lymph node or lymph node station 12c, is frequently incidentally removed during the index cholecystectomy. When removed, it potentially represents a prognosticator because the cystic duct node is the initial site of spread of gallbladder cancer in most patients with metastasis.[8–10] Kokudo et al. found that the cystic duct node was the most prevalent site of metastasis, involved in 92% of patients with the pN1 disease and 70.8% of patients with the pN2 disease.[11] However, it remains unclear whether the status of the cystic duct node by itself predicts the status of the D2 lymph nodes and thus indicates whether an OER is required. In this context, the extent of lymphadenectomy has been defined as D0 dissection when no lymph node is resected, D1 when the pericholedochal and hepatic hilum nodes (lymph node station 12) are resected, and D2 when nodes located along the common hepatic artery nodes (lymph node station 8) and peripancreatic lymph nodes (lymph node station 13) are removed with or without sampling of the paraaortic lymph node (lymph node station 16).

The aim of this study was to determine whether the status of the cystic duct node predicts the status of D2 lymph nodes and whether its status could determine if an extended lymph node dissection could be omitted.

Patients and Methods

We searched prospectively maintained databases at The University of Texas MD Anderson Cancer Center, Houston, TX, USA, and Hospital Sotero del Rio, Santiago, Chile, to identify all patients who were diagnosed with IGBC and subsequently underwent OER from June 1999 through June 2015. IGBC was defined as gallbladder cancer diagnosed after an open or laparoscopic cholecystectomy in a patient believed to have benign disease. A total of 230 patients met these inclusion criteria, of whom 40 patients were excluded because they had unresectable macroscopic residual cancer (remote organ metastases in 30 patients and extended locoregional disease in 10 patients), and 3 patients because they had concomitant cancer (colorectal cancer, renal cancer, and ampullary cancer in 1 patient each). The remaining 187 patients constituted the study population. This study was approved by the institutional review boards of both hospitals.

Before Re-resection (Oncologic Extended Resection)

Specimens and pathology reports from the primary cholecystectomy, often performed at an outside center, were reviewed by pathologists at Hospital Sotero del Rio or MD Anderson Cancer Center to confirm the diagnosis of gallbladder carcinoma. The T category, grade and differentiation, presence of perineural and lymphovascular invasions, status of the cystic duct and liver bed margins, and presence of metastases in adjacent lymph nodes were recorded.

Before re-resection, all patients underwent clinical assessment and radiographic staging of the disease, including computed tomography of the chest, abdomen, and pelvis and/or abdominal magnetic resonance imaging. An ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography scan was performed in some cases.

Chemotherapy or radiation therapy was administered before re-resection in certain cases following the recommendation of a multidisciplinary tumor board. At both institutions, OER was recommended to all patients with at least a tumor invasion beyond the lamina propia into the muscularis (T1b) without clinical evidence of remote organ metastases, as recommended by the National Comprehensive Cancer Network guidelines.[12]

Oncologic Extended Resection

At both institutions, re-resection was designed to achieve an R0 resection and appropriately stage the disease. The surgical procedure included the following:

1. Open or laparoscopic exploration and, in selected patients, intraoperative frozen section analysis of the aortocaval lymph nodes.
2. Limited resection of the liver bed or anatomical resection of liver segments IVb and V. In rare cases, major resection (≥3 Couinaud's segments) was performed.
3. Regional lymphadenectomy, including the removal of the hepatoduodenal ligament, hepatic artery, and retropancreatic lymph nodes.[13]

Regional lymph nodes were classified according to the TNM classification of the American Joint Committee on Cancer, the Japanese Classification of Gastric Carcinoma,[14] and the General Rules for Surgical and Pathological Studies on Cancer of Biliary Tract.[15] Disease in the pericholedochal and hepatic hilum nodes (lymph node 12) was considered N1, and disease in the common hepatic artery nodes (lymph

Table 1 Patient characteristics overall and by status of the cystic duct lymph node

Characteristic	Total	Positive cystic duct node	Negative cystic duct node	Unknown status of cystic duct node	*P* value (positive vs negative)[b]	*P* value (positive vs negative vs unknown)[b]
All patients	187	29	44	114		
Sex, M:F	49:138	5:24	12:32	32:82	0.241	0.512
Age, median (range), years	60 (32–81)	58 (39–76)	61 (32–77)	60 (33–81)	0.821[c]	0.974[c]
First cholecystectomy						
Jaundice before surgery	12 (6.4)	1 (3.4)	3 (7)	8 (7)	0.510	0.916
Acute cholecystitis before surgery	84 (45)	12 (41.3)	19 (43)	53 (46.4)	0.378	0.307
Cholelithiasis at surgery	138 (74)	18 (62)	31 (70.4)	89 (78)	0.611	0.269
Laparoscopic cholecystectomy	125 (67)	19 (66)	31 (70.4)	75 (66)	0.423	0.881
Well/moderately/poorly differentiated[a]	32/113/25	6/20/1	4/29/7	22/64/17	0.151	0.209
T category, T1/T2/T3	25/125/37	1/23/5	5/30/9	19/72/23	0.481	0.399
Perineural and/or lymphovascular invasions	78 (42)	19 (66)	14 (32)	45 (39.4)	*0.005*	*0.008*
Liver bed margin-positive	22 (12)	5 (17.2)	6 (14)	11 (10)	0.218	0.288
Cystic duct margin-positive	23 (12.2)	4 (14)	2 (5)	17 (15)	0.112	0.137
Second radical resection						
Preoperative chemotherapy	11 (6)	6 (21)	2 (5)	3 (3)	*0.039*	*0.004*
Preoperative radiation therapy	7 (4)	4 (14)	1 (2.3)	2 (2)	0.077	*0.025*
Interval between the first and second surgeries, median (range), days	72 (11–333)	72 (16–333)	70 (21–329)	74 (11–330)	0.371[c]	0.3411[c]
Main procedures						
Segment IVb + V resection	179 (96)	27 (93.1)	42 (95.4)	110 (96.4)	0.735	0.571
Major liver resection	8 (4.2)	2 (7)	2 (5)	4 (4)		
Combined resection						
Common bile duct	48 (26)	8 (28)	8 (18)	32 (28)	0.253	0.437
Adjacent organ	17 (9.1)	5 (17.2)	2 (5)	10 (9)	0.083	0.219
Hepatic artery and/or portal vein	9 (5)	1 (3.4)	1 (2.3)	7 (6.1)	0.640	0.491
Lymph node removal						
Hepatic pedicle dissection	180 (96)	27 (93.1)	44 (100)	109 (96)	0.154	0.278
Hepatic artery dissection	158 (85)	24 (83)	39 (89)	95 (83.3)	0.491	0.798
Pancreaticoduodenal dissection	94 (50.2)	15 (52)	21 (48)	58 (51)	0.420	0.910
Paraaortic sampling	106 (57)	19 (66)	21 (48)	66 (58)	0.052	0.183
Estimated blood loss, median (range), cc	200 (50–2000)	150 (50–2000)	200 (50–1500)	200 (50–1800)	0.704[c]	0.514[c]
Operative time, median (range), min	240 (60–600)	240 (60–510)	210 (60–450)	250 (75–600)	0.273[c]	0.406[c]
Any complication	36 (19.3)	1 (3.4)	5 (11.4)	30 (26.3)	0.254	*0.005*
Complication, Clavien-Dindo grade ≥IIIa	18 (10)	0	2 (5)	16 (14)	0.353	0.037
90-day mortality	2 (1.1)	0	0	2 (1.8)	1	1
Postoperative hospital stay, median (range), days	6 (1–52)	6 (3–12)	5 (1–25)	6 (3–52)	*<0.001*[c]	*<0.001*[c]
Surgical margin status, R1	17 (9.1)	2 (7)	3 (7)	12 (11)	0.665	0.765
Residual cancer	73 (39)	16 (55.2)	13 (30)	43 (38)	*0.026*	0.085
Lymph node	43 (23)	14 (48.3)	4 (9)	25 (22)	*0.001*	*0.002*
Liver parenchyma	21 (11.2)	5 (17)	3 (7)	13 (11.4)	0.164	0.428
Bile duct	11 (6)	3 (10.3)	3 (7)	5 (4.4)	0.425	0.370
Distant organ	5 (3)	0	1 (2.3)	4 (4)	0.603	0.830
Number of lymph nodes retrieved, median (range)	6 (0–27)	6 (1–16)	5 (0–19)	5 (0–27)	0.780[c]	*0.015*[c]
Final N1/N2	44/16	23/5	3/1	18/10	*<0.001*	*<0.001*
Final M1	4 (2.1)	0	1 (2.3)	3 (3)	0.603	1
UICC 7th edition stage, I/II/III/IV	14/86/69/18	0/0/24/5	3/29/10/2	11/57/35/11	*<0.001*	*<0.001*
Postoperative chemotherapy	44 (24)	13 (45)	8 (18.1)	23 (20.1)	*0.014*	*0.020*

Table 1 (continued)

Characteristic	Total	Positive cystic duct node	Negative cystic duct node	Unknown status of cystic duct node	*P* value (positive vs negative)[b]	*P* value (positive vs negative vs unknown)[b]
Postoperative radiation therapy	12 (6.4)	3 (10.3)	2 (5)	7 (6.1)	0.308	0.575
Recurrence	62 (34)	16 (55.1)	13 (30)	34 (30)	*0.026*	0.034

Values in the table are the number of patients (percentage) unless indicated otherwise. The italics means that the *p* value is equal or less to 0.05

UICC Union for International Cancer Control

[a] Only 170 observations

[b] χ^2 test, unless indicated otherwise

[c] Wilcoxon rank-sum test

node 8) and peripancreatic lymph nodes (lymph node 13 and 16) was considered N2. If the cholecystectomy specimen included a lymph node, that node was assumed to be the cystic duct node. When the specimen included two nodes, both were assumed to be cystic duct nodes. In patients with two cystic duct nodes retrieved, nodal status was negative if both nodes were free of disease and positive if one or both nodes contained disease. Common bile duct resection was performed only in patients with a positive cystic duct stump margin after re-resection or macroscopic tumor invasion. Combined resection of adjacent organs was performed selectively to achieve R0 resection. Resection of the port site was performed in rare cases according to the surgeon's preference and clinical indication.

Management After Oncologic Extended Resection

The disease was staged according to the American Joint Committee on Cancer clinical staging system for gallbladder cancer, seventh edition.[16] R0 resection was defined as a resection with macroscopically and microscopically tumor-free margins, and R1 was defined as microscopically positive margins. Residual cancer was defined as the presence of any pathologically proven cancer tissue in the lymph nodes, liver parenchyma, bile duct, or distant organs at the time of re-resection. Surgical complications were defined as any deviation from the normal postoperative course within 90 days after re-resection and were scored using the Clavien-Dindo system.[17] Postoperative deaths were defined as deaths occurring within 90 days after surgery.[18]

Statistical Analysis

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 test. Disease-specific survival (DSS) was measured from the date of re-resection to the date of death due to gallbladder cancer or last follow-up. The prognostic relevance of a positive cystic duct node was analyzed separately from the prognostic relevance of the pN1 status. Pathologic nodal status was correlated with DSS. Survival curves were generated using the Kaplan-Meier method, and the differences between curves were evaluated with the log-rank test. Univariate analyses to identify predictors of survival and disease in different lymph nodes were performed by using the Cox proportional hazard regression models. $P < 0.05$ was considered statistically significant in all analyses. Statistical analyses were performed using the program Stata 13 for Windows (Texas; StataCorp LP).

Results

The characteristics of the 187 patients included in the study are summarized in Table 1. The median age was 60 years (range, 32–81). Forty-nine patients (26%) were male, and the female:male ratio was 2.8 to 1. Eighty-four patients (45%) had acute cholecystitis diagnosed before index cholecystectomy, and 125 (67%) had laparoscopic index cholecystectomy. The T category was T1 in 25 patients, T2 in 125, and T3 in 37. The median interval between the first and second surgeries was 72 days (range, 11–333). At the second surgery, 179 patients (96%) had gallbladder bed resection or resection of hepatic segments IVb and V; only eight patients (4.2%) underwent major liver resection. Seventeen patients (9.1%) had R1 resection. A total of 1261 lymph nodes was retrieved; the median number of nodes retrieved per patient was 6.4 (range, 0–27). Common bile duct resection ($n = 48$) did not increase the number of retrieved lymph nodes. The preoperative and postoperative chemotherapy and chemoradiotherapy did not show a survival benefit in the Cox regression model for the entire cohort, $p = 0.518$ and $p = 0.102$ (Supplementary Table 1). While our data demonstrates that there was no survival benefit, the statistically significantly increased HR in the postoperative radiation group suggests that we were able to

Table 2 Risk of lymph node metastases by location in patients with a positive cystic duct node

Lymph node location	Odds ratio	95% CI	*P* value
Hepatic pedicle	5.2	1.4–19	*0.012*
Common hepatic and/or peripancreatic			0.026
Hepatic artery (LNS 8)	1	0.3–1.3	0.227
Pancreaticoduodenal (LNS 13)	1	0.3–2.0	0.638
Paraaortic (LNS 16)	1	0.2–2504	0.214

The italics means that the *p* value is equal or less to 0.05

LNS lymph node station

accurately identify high-risk patients from the OER for consideration of additional therapy.

Patient Characteristics by Cystic Duct Node Status

Seventy-three patients (39%) had a cystic duct node retrieved at the time of the index cholecystectomy (Table 1). Compared to patients with negative cystic duct nodes, patients with positive cystic duct nodes had higher rates of perineural and/or lymphovascular invasions (66 vs 32%, $p = 0.005$), neoadjuvant chemotherapy (21 vs 5%, $p = 0.039$), residual cancer (55.2 vs 30%, $p = 0.026$), residual cancer in lymph nodes (56 vs 13%, $p = 0.001$), postoperative chemotherapy (45 vs 18%, $p = 0.014$), and recurrence (55 vs 30%, $p = 0.026$).

Relationship Between a Positive Cystic Duct Node and Disease Status of Other Lymph Nodes

Twelve patients (6.4%) had a D0 nodal dissection, 27 (14.4%) had a D1 nodal dissection, and 148 (79%) had a D2 nodal dissection. D2 dissection identified skipped lymph node metastases in 24 patients (13%). A positive cystic duct node was associated with an increased likelihood of positive hepatic pedicle lymph nodes (odds ratio [OR] 5.2, $p = 0.012$) but was not correlated with the status of the common hepatic artery nodes, pancreaticoduodenal nodes, or paraaortic nodes, when we analyzed each station separately (Table 2). Compared to patients with negative nodes, patients with a positive cystic duct node before OER had worse DSS (hazard ratio [HR] 2.09 [95% CI 1.09–4.01], $p = 0.026$), but if no residual cancer was detected on OER, the HR was 1.5 (95% CI 0.64–3.6, $p = 0.337$) (Table 3). The HR in patients with positive D1 nodes was 6.07 (95% CI 2.2–21, $p = 0.001$), whereas the HR in patients with positive D2 nodes was 13.8 (95% CI 1.69–101, $p = 0.014$) (Table 4).

Table 4 Hazard ratio by location of positive lymph nodes

Location of positive nodes	Hazard ratio	95% CI	*P* value
Cystic lymph node	2.09	1.1–4.01	*0.026*
Hepatic pedicle	6.07	2.2–21	*0.001*
D2 lymph nodes	13.8	1.69–101	*0.014*
Hepatic artery (LNS 8)	15.8	1.4–174.5	*0.024*
Pancreaticoduodenal (LNS 13)	3.9	0.85–17.1	0.079
Paraaortic (LNS 16)	2.36	0.45–12.2	0.304

The italics means that the *p* value is equal or less to 0.05

LNS lymph node station.

Patient Characteristics by N Category

Of the 187 patients in the study, 127 had N0 disease, 17 had only cystic duct nodal metastases, 27 had N1 disease involving nodes other than the cystic duct node, and 16 had N2 disease. The characteristics of patients by nodal status are summarized in Table 5. Compared to patients in the other groups, the patients with N2 disease had higher preoperative CA 19-9 level, higher rate of preoperative chemotherapy, longer intervals between the first and second surgeries, higher rate of resection of the pancreaticoduodenal lymph nodes, higher estimated blood loss at re-resection, longer postoperative hospital stay, and higher rate of residual cancer in the bile duct, although this last difference was not significant. Perineural and/or lymphovascular invasions and a positive liver bed margin were more common in patients with positive cystic duct lymph node or N1 disease than in patients in the other groups.

DSS by Lymph Node Status

The 3- and 5-year DSS rates for the entire cohort were 68.9% (95% CI 60.3–76.1%) and 60.1% (95% CI 51–68%), respectively. The 3-year DSS rate was 75% (95% CI 58.6–85.8%)

Table 3 Hazard ratio by N status for patients

N status	Hazard ratio[a]	95% CI	*P* value
N0	1	1	
Cystic duct node-positive	2.09/1.5[b]	1.09–4.0/0.64–3.6[b]	*0.026*/0.337[b]
N1	2.6	1.5–4.8	*0.001*
N2	5.9	3.2.-11.2	*<0.001*

The italics means that the *p* value is equal or less to 0.05

[a] Cox regression

[b] Without RC

Table 5 Patient characteristics overall and by N status

Characteristic	N0	Metastasis in cystic duct node only	N1	N2	*P* value (N0 vs cystic node+ vs N1 vs N2)[c]
All patients	127	17	27	16	
Sex, M:F	39:88	2:15	4:23	4:12	0.192
Age, median (range), years	61 (32–77)	55 (43–68)	61 (42–81)	56 (33–70)	0.758[d]
First cholecystectomy					
Jaundice before surgery	7 (6)	1 (6)	1 (4)	3 (19)	0.125
Acute cholecystitis before surgery	54 (43)	6 (35.2)	17 (63)	7 (44)	0.256
Cholelithiasis at surgery	94 (74)	9 (53)	23 (85.1)	12 (75)	0.339
Laparoscopic cholecystectomy	89 (70)	10 (59)	20 (74)	6 (38)	0.054
Well/moderately/poorly differentiated[a]	22/72/20	3/12/1	4/18/2	3/11/2	0.904
T category, T1/T2/T3	19/84/24	0/15/2	1/18/8	5/8/3	0.069
Preoperative CA 19-9 level, median (range), U/ml[b]	19 (1–67)	16 (2.8–45)	18 (1–103)	36 (9.5–4000)	*<0.001*
Perineural and/or lymphovascular invasions	45 (35.4)	10 (59)	17 (63)	6 (38)	*0.013*
Liver bed margin-positive	10 (8)	3 (18)	6 (22.2)	3 (19)	*0.016*
Cystic duct margin-positive	13 (10.2)	1 (6)	4 (15)	5 (31.2)	0.089
Second radical resection					
Preoperative chemotherapy	3 (2.4)	2 (12)	3 (11.1)	3 (19)	*0.009*
Preoperative radiation therapy	3 (2.4)	1 (6)	2 (7.4)	1 (6.3)	0.236
Interval between the first and second surgeries, median (range), days	72 (11–329)	71 (16–199)	80 (32–333)	82 (16–146)	*<0.001*[d]
Main procedures					
Segment IVb + V resection	121 (95)	16 (94)	27 (100)	15 (94)	0.341
Major liver resection	6 (5)	1 (6)	0	1 (6.3)	
Combined resection of adjacent organ					
Common bile duct	27 (21.2)	4 (24)	12 (44.4)	5 (31.3)	0.090
Adjacent organ	10 (8)	3 (18)	1 (4)	3 (19)	0.169
Hepatic artery and/or portal vein	5 (4)	0	1 (4)	3 (19)	0.152
Lymph node removal					
Hepatic pedicle dissection	123 (97)	16 (94.1)	25 (96)	16 (100)	0.778
Hepatic artery dissection	109 (86)	15 (88.2)	19 (70.4)	15 (94)	0.469
Pancreaticoduodenal dissection	57 (45)	8 (47)	14 (52)	15 (94)	*0.002*
Paraaortic sampling	69 (54.3)	12 (71)	11 (41)	14 (88)	*0.015*
Estimated blood loss, median (range), cc	200 (50–1800)	205 (50–400)	200 (50–1550)	700 (125–2000)	*0.001*[d]
Operative time, median (range), min	240 (60–530)	240 (180–450)	235 (60–600)	248 (165–560)	0.318[d]
Any complication	28 (22)	1 (6)	4 (15)	3 (19)	0.424
Complication, Clavien-Dindo grade ≥IIIa	15 (12)	0	1 (4)	2 (13)	0.331
90-day mortality	1 (1)	0	0	1 (6.3)	0.219
Postoperative hospital stay, median (range), days	6 (1–37)	6 (3–12)	6 (3–14)	7 (3–52)	*<0.001*[d]
Surgical margin status, R1	7 (6)	1 (6)	6 (22.2)	3 (19)	0.016
Residual cancer	26 (21)	4 (24)	27 (100)	16 (100)	*<0.001*
Liver parenchyma	12 (9.4)	3 (18)	4 (15)	2 (13)	0.574
Bile duct	5 (4)	1 (6)	2 (7.4)	3 (19)	0.089
Distant organ	4 (3.1)	0	1 (4)	0	1
Number of lymph nodes retrieved, median (range)	5 (0–20)	6 (1–16)	6 (1–27)	11 (3–18)	0.562[d]
Final M1	3 (2.3)	0	1 (4)	0	0.791
UICC 7th edition stage, I/II/III/IV	14/86/25/2	0/0/17/0	0/0/27/0	0/0/0/16	*<0.001*
Postoperative chemotherapy	20 (16)	5 (29.4)	15 (56)	4 (25)	*<0.001*
Postoperative radiation therapy	5 (4)	1 (6)	5 (19)	1 (6.2)	*0.042*
Recurrence	32 (25)	10 (59)	14 (52)	7 (44)	*0.003*

Values in the table are the number of patients (percentage) unless indicated otherwise. The italics means that the *p* value is equal or less to 0.05

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[a] Only 170 observations

[b] Only patients from MD Anderson Cancer Center

[c] χ^2 test, unless indicated otherwise

[d] Wilcoxon rank-sum test

for patients with a negative cystic duct node, 38% (95% CI 19.5–57.3%, $p = 0.011$) for patients with a positive cystic duct node, and 58% (95% CI 47.3–67.1%, $p = 0.147$) for patients with unknown cystic duct nodal status (Fig. 1). When the patients were stratified by the TNM categories of nodal status, the 3-year DSS rates were 70% (95% CI 60–78%) for patients with N0 disease, 60% (95% CI, 31–80%, $p = 0.337$) for patients with a positive cystic duct node, 31% (95% CI 14–50%,

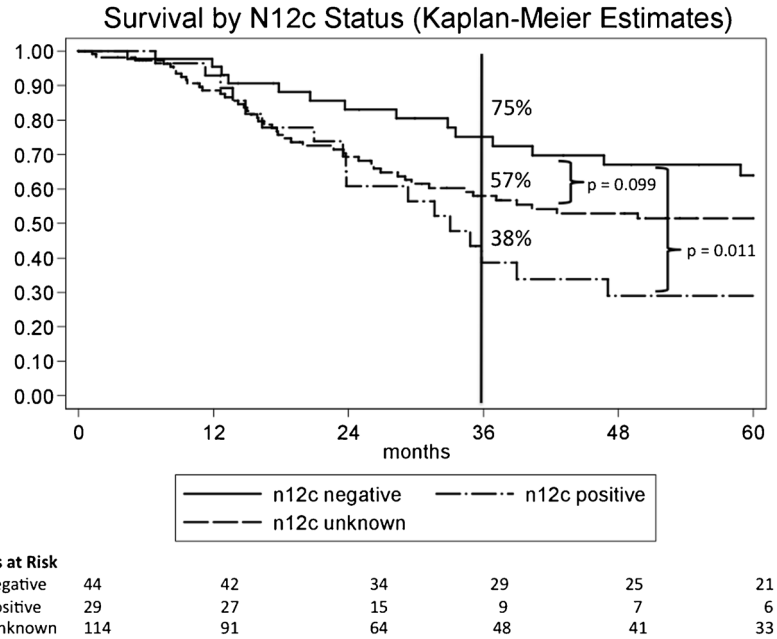

Fig. 1 Disease-specific survival (DSS) of the entire cohort according to the status of the cystic duct lymph node from the index cholecystectomy

$p = 0.01$) for patients with N1 disease, and 14% (95% CI 2.3–36%, $p < 0.001$) for patients with N2 disease (Fig. 2).

The presence of three or more positive lymph nodes dramatically reduced the median DSS (HR 6.1 [95% CI 3.08–12.11], $p < 0.001$). The 3-year DSS rate was 63% (95% CI 54–70%) in patients with two or fewer positive lymph nodes vs 0% in the patients with three or more positive lymph nodes ($p < 0.001$) (Fig. 3). The total lymph node count during OER had no impact on DSS, even in the subgroup of patients with N0 disease (HR 1.06, 95% CI 0.98–1.15).

Discussion

Our findings indicate that the status of the cystic duct node can predict the status of the hepatic pedicle nodes but not the presence or absence of more advanced lymphadenopathy in patients with IGBC. Conversely, in patients without residual cancer at OER (favorable tumor biology indicator), patients with disease in the incidental cystic duct node only and patients with completely negative lymph nodes may have similar DSS. Due to these findings, the status of the cystic duct node

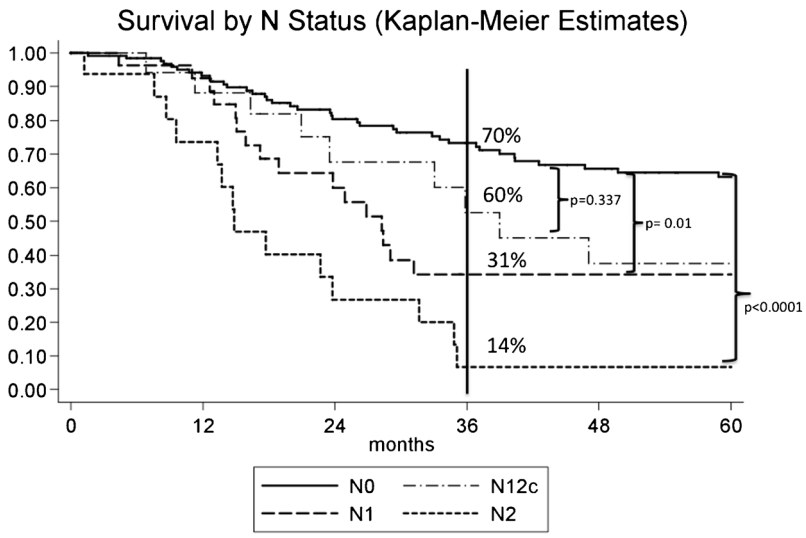

Fig. 2 Disease-specific survival (DSS) of the entire cohort by pathologic nodal status after OER

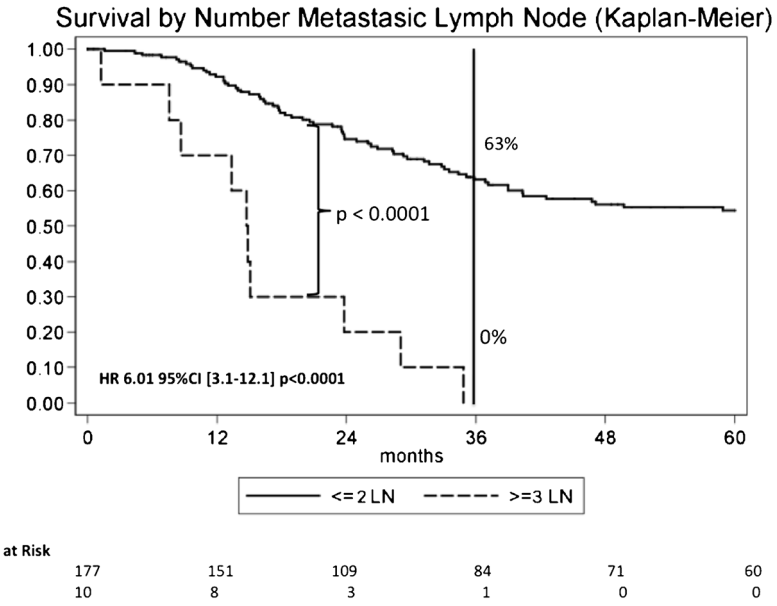

Fig. 3 Disease-specific survival (DSS) of the entire cohort according to number of positive lymph nodes

cannot substitute for the completion of OER. Finally, we found that higher preoperative CA 19-9 level (mean 35 U/ml, $p < 0.001$), higher rates of perineural and/or lymphovascular invasions, and higher rates of positive liver bed margins predicted pN2 disease. This information highlights the importance of these factors, which are determined immediately after the primary cholecystectomy, in predicting positive pN2 stations, which can be removed only with a OER. We also found that the risk of death from gallbladder cancer increased with an increasing number of metastatic lymph nodes. In fact, no patient with four or more positive lymph nodes survived 3 years, similar to what was found in a previous study.[19]

Our findings suggest that D2 lymph node dissection is needed for accurate staging and therefore should be recommended for all patients undergoing OER. Our findings agree with previously published findings indicating that the higher number of lymph nodes harvested at OER correlates with more accurate staging,[20·21] but differs from previous reports[22–24]; in that, the higher total lymph node count during OER did not correlate with better DSS, even in the subgroup of patients with N0 status. Further, while previous studies have suggested that the location of lymph node metastases performs poorly in predicting long-term survival,[21·23·25·26] our report demonstrates that patients with positive hepatic pedicle and hepatic artery nodes had very different DSS compared to pN0 status (HR 6.07 [95% CI 2.2–21], $p = 0.001$, and HR 15.8 [95% CI 1.4–174.5], $p = 0.024$, respectively).

This study has several limitations. First, while this is a retrospective study, the data were prospectively collected, and this limitation is common to all published series to date on gallbladder cancer. Second, the pathology report from the index cholecystectomy did not report the status of perineural and/or lymphovascular invasions in 53 patients (28%), the liver margin in 43 patients (23%), the cystic duct margin in 34 patients (18%), or the histologic differentiation in 17 patients (9%). Third, our finding suggests (Table 2) that paraaortic lymph node metastases performed poorly in predicting long-term DSS (HR 2.36, CI 0.45–12.2, $p = 0.304$) which is different from previously published series.[27] A possible reason is that 79 patients (42%) did not have paraaortic nodal sampling, which was common at the beginning of our study period.

Conclusions

Our findings indicate that the status of the cystic duct node can predict the status of the hepatic pedicle nodes but not the presence or absence of more advanced lymphadenopathy. Conversely, when no residual cancer is found at OER (favorable tumor biology indicators), patients with disease in the incidental cystic duct node only and patients with completely negative lymph nodes may have similar DSS. Due to these findings, the status of the cystic duct node cannot substitute for OER. Our data show that D2 lymph node dissection is needed for accurate staging and stratification in low-risk (<3 lymph nodes) and high-risk (≥3) groups. Therefore, we recommend D2 lymph node dissection for all patients undergoing OER.

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Author Contributions All authors meet the following criteria:

1. Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.

Vega, Vinuela, Yamashita, Sanhueza, Cavada, Diaz, Aloia, Chun, Tzeng, Okuno, Goumard, Vauthey, Lee, and Conrad.

2. Drafting the work or revising it critically for important intellectual content.

Vega, Vinuela, Yamashita, Sanhueza, Cavada, Diaz, Aloia, Chun, Tzeng, Okuno, Goumard, Vauthey, Lee, and Conrad.

3. Final approval of the version to be published.

Vega, Vinuela, Yamashita, Sanhueza, Cavada, Diaz, Aloia, Chun, Tzeng, Okuno, Goumard, Vauthey, Lee, and Conrad.

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Vega, Vinuela, Yamashita, Sanhueza, Cavada, Diaz, Aloia, Chun, Tzeng, Okuno, Goumard, Vauthey, Lee, and Conrad.

Compliance with Ethical Standards This study was approved by the institutional review boards of both hospitals.

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

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