Bile duct/Gallbladder

Surgery in node-positive gallbladder cancer: The implication of an involved superior retro-pancreatic lymph node

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A R T I C L E   I N F O

A B S T R A C T

Background: The treatment approach to node-positive gallbladder cancer has unresolved issues with regard to the management of patients with a positive superior retro-pancreatic (level 13a) node, which is the highest level of spread. The American Joint Committee on Cancer remains unclear on the status of the 13a node.
Methods: This retrospective study consisted of 165 patients with node-positive gallbladder cancer without distant metastasis. Patients were reclassified according to the American Joint Committee on Cancer eighth edition classification. The survival of patients with positive level 13a node was compared with that of patients with N1 disease (T stage-wise) and those with para-aortic nodal disease. A multivariate analysis was performed for factors affecting survival.
Results: The 5-year survival of patients with positive level 13a with 1–3 nodes was similar to those with N1 disease (40.2% and 32.9%, respectively) and was better than those with more distant nodal spread ($P < .05$). In univariate and multivariate analyses, intraoperative blood loss (hazard ratio [HR] 1.58), R1 resection (HR 1.87), and T4 disease (versus T2, HR 3.44) were poor prognosticators. Pancreaticoduodenectomy may be beneficial in T2 patients.
Conclusion: A positive superior retro-pancreatic node does not worsen the prognosis in an otherwise N1 disease in T1/T2 gallbladder cancer. It behaves like a regional lymph node and should be treated as such.

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Introduction

Node-positive gallbladder cancer (CaGB) has a poor prognosis. The new American Joint Committee on Cancer (AJCC) classification (eighth edition) has subclassified regional lymph nodes (LNs) of CaGB into N1 (1–3 regional LNs) and N2 (≥4). Patients with N2 nodal disease are now classified as stage 4b along with patients with metastatic disease, implying the grave prognosis with increased nodal burden.[1]

The lymphatic drainage from the gallbladder descends along the cystic duct to the nodes around the common bile duct and then to the nodes along the posterosuperior part of the pancreas. They may also descend from the pericholedochal nodes to the nodes along the portal vein and hepatic artery. From these areas, they drain into the periaortic nodes.[2,3]

The superior retro-pancreatic (level 13a) LN is considered to be N2 disease.[1,4-6] It has always been a matter of ambiguity among surgeons whether to consider this node as regional and continue with curative surgery in a patient with otherwise localized disease or abandon the procedure, considering it to be advanced disease. The level 13a LN is not mentioned in the latest AJCC staging for CaGB. The extent of regional lymphadenectomy in CaGB is thus still not standardized worldwide.[3,4,7]

We classified our patients under the new AJCC classification and studied those with level 13a node disease as the furthest echelon of spread. None of the patients we studied had metastatic disease. We compared the survival of CaGB patients with positive level 13a LN with that of patients classified as having N1 and N2 disease by the latest AJCC classification.[1]

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Methods

This study was approved by the Institutional Review Board of Tokyo Women's Medical University (approval number: 4328-R), and the need for informed consent was waived because this was a retrospective chart review analysis.

From 1974 to 2016, a total of 426 patients underwent surgical resection for CaGB in our institute. Of these patients, 165 patients had positive regional or level 13a LNs without distant metastasis. These patients had undergone surgery in the form of radical cholecystectomy with removal of a cuff of liver or segments 4a/5 with regional or extended LN dissection. Major hepatectomy (resection of 3 or more segments) or pancreaticoduodenectomy (PD) were performed to achieve negative margins. PD was also performed for regional nodal clearance in the case of level 13a LN infiltrating the pancreas when a dissection was not possible or when LN metastasis around the pancreas was predicted and a dissection was not possible. Fifty-five patients underwent PD. Of these, 36 patients (65%) had bile duct invasion and nodal involvement and 19 patients (35%) had nodal involvement without bile duct invasion.

Until 1996 we actively performed PD when the depth of mural cancer and its location indicated the possibility of LN metastasis.[8] Beginning in 1997, we tried not to perform simultaneous major hepatectomy and pancreaticoduodenectomy (HPD) for advanced CaGB because the morbidity and mortality rates of this surgery were very high.[8]

All patients underwent dissection of LNs along the hepatoduodenal ligament, common hepatic artery, and retro-pancreatic region. LNs along the interaortocaval region were sampled. Before the year 2000, many patients (especially if PD was done) underwent para-aortic dissection. Celiac LNs were dissected if they were found enlarged intraoperatively. Bile duct resection (BDR) was performed if the bile duct was involved, for achieving negative tumor margins or for adequate LN clearance if needed. Portal vein and hepatic artery resection with reconstruction were done if they were involved with the disease.

In our institute, ultrasonography, computed tomography (CT), multidetector row CT and positron emission tomography CT were introduced in 1984, 1986, 2005, and 2005, respectively. Thus patients had undergone preoperative evaluation with the best available modality during that era. Patients were monitored every 3 months until 3 years after surgery. Recurrence was determined using tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) at every follow-up in addition to ultrasound or CT scan.

Postoperative morbidity was assessed using Clavien-Dindo classification.[9] Adjuvant therapy was administered according to the clinician's discretion based on LN status, residual disease, and performance status of the patient. Adjuvant therapy consisted of titanium silicate 1 (since 2002) or gemcitabine (since 2003) within 12 weeks postoperatively. Before 2002, no patient received adjuvant chemotherapy.

Among 165 patients, 17 died in hospital postoperatively (7 had undergone major HPD, 4 major hepatectomy, and 2 PD). All but 2 of the postoperative deaths were before the year 2000. We excluded these postoperative deaths from our study. The final study population consisted of 148 patients, 62 men and 86 women. Thirty-nine patients underwent major hepatectomy, 39 underwent resection of segments 4a plus 5, 39 had extended cholecystectomies with liver cuff, and 31 patients underwent simple cholecystectomy. All patients underwent standard or extended lymphadenectomy.

Among the 55 patients in whom PD was performed, 12 patients had undergone major HPD (resection of 3 or more segments of liver and pancreaticoduodenectomy), 23 patients underwent resection of segments 4a/5 of the liver, and 15 underwent an extended cholecystectomy. Five patients underwent PD alone. Twenty-seven patients underwent major hepatectomy and BDR without PD. BDR was performed in 56 patients, and vascular resection was performed in 25 (22 portal vein and 3 hepatic artery resection and reconstruction).

In 48 patients (32%), the resection margins were positive microscopically.

Only 20% received adjuvant chemotherapy. The average number of LNs dissected was 12.7. In patients who underwent PD, the average number dissected lymph nodes was 22.6.

The patients were reclassified according to AJCC eighth edition classification and broadly divided into 5 groups as follows:

Group N1: any T, N1 (1–3 regional LNs), M0 ($n = 69$)
Group N2: any T, N2 (≥ 4 regional LNs), M0 ($n = 10$)
Group N13e: any T, N (positive level 13a with or without regional nodes; total nodes 1–3), M0 ($n = 26$)
Group N13adv: any T, N (positive level 13a with or without regional nodes; total nodes ≥ 4), M0 ($n = 13$)
Group N14: any T, N (level 14–17 node positive with or without regional LN), no distant metastasis ($n = 30$)

For survival analysis, we included N2 patients and N13adv patients together because the number of patients were few.

Statistics

Differences in the qualitative variables between groups were determined via the Fisher exact (2-sided) test using the R environment (Version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria) and SPSS statistical package (Version 25.0J; IBM

Table 1
Different nodal groups and survival rates.

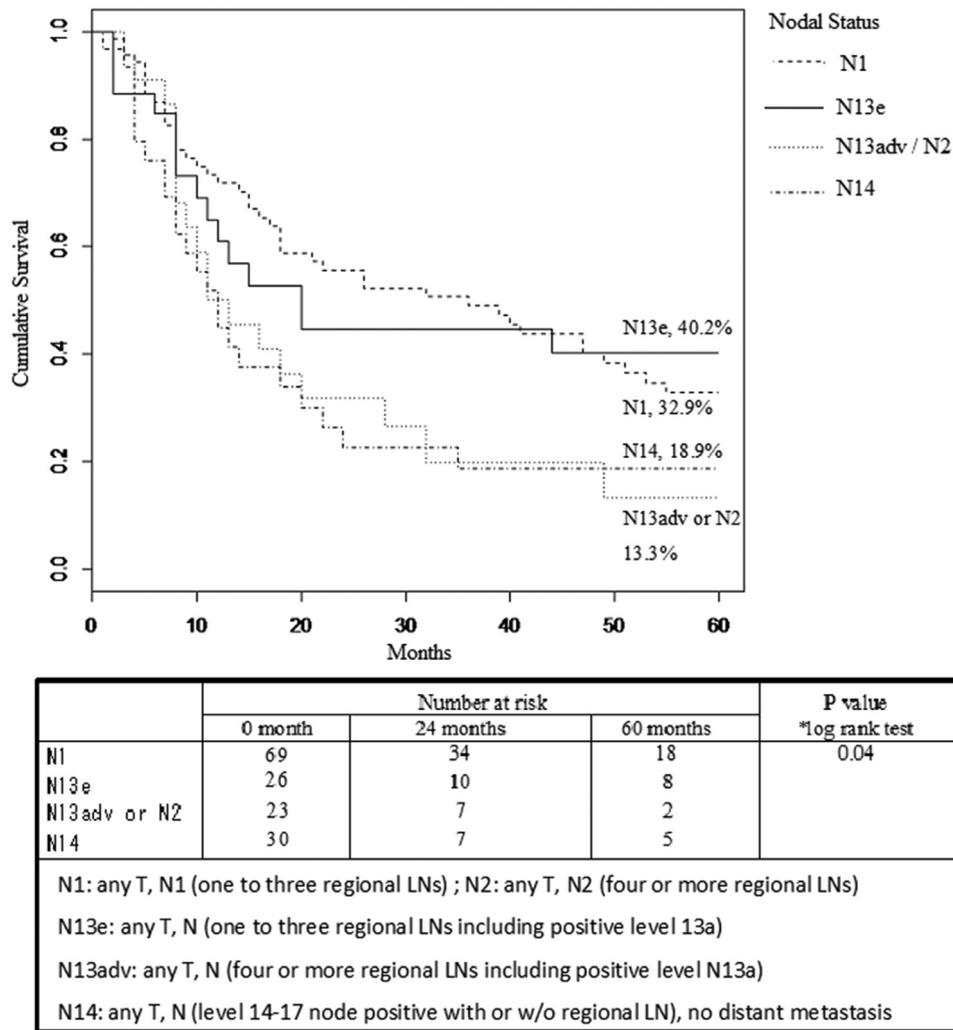|	Patient no.	Median survival (months)	2-y survivors	5-y survivors
N1	69	36	34	17 (25%)
T1/T2	24	66	17 (71%)	13 (54%)
T3	26	39	13 (50%)	4 (15%)
T4	19	16	4 (21%)	0
N13e	26	15	11	8 (31%)
T1/T2	12	142	8 (67%)	7 (58%)
T3	7	15	2 (29%)	0
T4	7	8	1 (14%)	1 (14%)
N13adv	13	11	3 (23%)	1 (8%)
N2	10	18	4 (40%)	1 (10%)
N14	30	12	7 (23%)	5 (17%)

Fig. 1. Overall survival rates of different nodal groups.

Corp, Armonk, NY). We compared the survival of patients between groups N1 and N13e for the different T stages. We then compared the survival of group N13e with N13adv, N2, and N14. Kaplan-Meier curves were plotted, and univariate and multivariate analyses were performed using the Cox proportionate hazard model to know whether there were other factors that influenced the outcome. Only factors that were significant in univariate analysis were used for multivariate analysis.

Results

The median survival in the N1 group was 36 months compared with 20 months in the N13e group (Table 1). However, the 5-year survival was similar in both groups (32.9% and 40.2%, respectively; Fig 1) and were better than those with more distant nodal spread (Fig 1; $P < .05$). When patients with T1 and T2 disease were considered, the 5-year survival of patients in the N13e group was 58%, which was comparable to 54% in the N1 group. Across all other groups, the 5-year survival was poor (Table 1). Among patients in the N13e group, those with T2 disease had better survival than those with T3 or T4 disease. The survival of patients with N1 disease has also been plotted for comparison (Figs 2 and 3). When we compared our patients before and after the year 2000, the percentage of patients with N1 nodes was significantly greater in the group of patients who underwent surgery after the year 2000, al-

though there was no difference in the frequency of metastasis to other LNs (N13e, N13adv, N2, N14; Supplemental Table 1).

In univariate and multivariate analysis, intraoperative blood loss (hazard ratio [HR] 1.58), positive resection margins (HR 1.87), and T4 disease (versus T2; HR 3.44) were significant independent prognosticators for overall survival (OS; Table 2). There was no significant difference in survival between the N13e and N1 groups in multivariate analysis.

Among 100 patients with R0 resection, recurrence was more common in patients in the N2 group (6 of 6 patients), the N14 group (92%, 12/13), and the N13adv group (78%, 7/9) compared with the N1 (67%, 35/57) and N13e groups (26%, 4/15). Locoregional and distant metastasis occurred with similar frequency.

In the N14 group, the outcome of patients was poor, although there were 5 long-term survivors out of 30 patients. All 5 patients had undergone PD (2 PD, 2 PD with extended cholecystectomy, and 1 major HPD) and no patient had T4 disease (Table 3).

Although treatment with PD was not a significant factor for OS (Table 2), 18 of 55 patients with node-positive CaGB who underwent PD survived more than 5 years (Table 3). Among patients who underwent PD without major hepatectomy, 17 of 43 survived for more than 5 years. Of these, most survivors had T2 disease (Table 3). When patients with T2 and node-positive disease were analyzed separately, performance of PD and surgery performed after the year 2000 ($P = .005$, $P = .03$, respectively) were associated with a better survival.
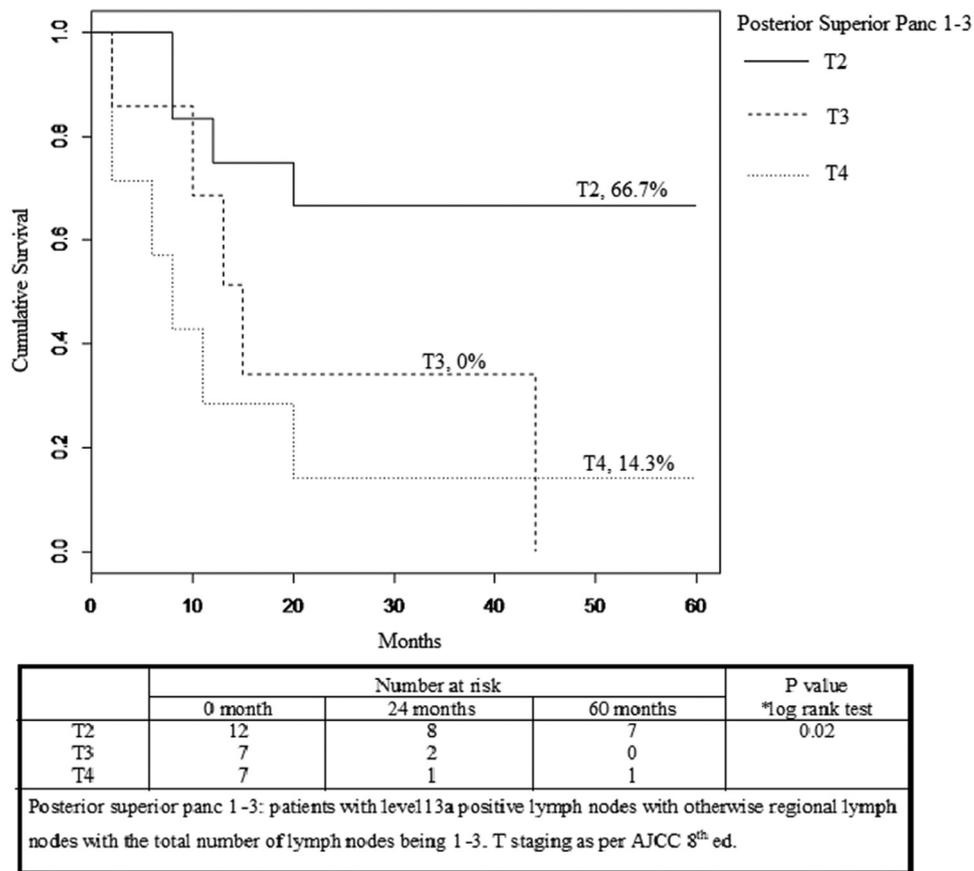
Fig. 2. Overall survival rates in patients with 13a node-positive gallbladder cancer (1–3 nodes in 13a and regional LNs), by T stage. *AJCC,* American Joint Committee on Cancer.

Among patients who underwent PD without major hepatectomy, 2 died postoperatively. There were no postoperative deaths among these patients after the year 2000. The postoperative morbidity rates decreased from 60% to 40% after the year 2000. Among 12 patients who underwent major HPD without postoperative mortality, the median survival was 10 months, with only 1 patient surviving more than 2 years (long-term survivor). In patients who underwent major hepatectomy without PD, the mortality rates have decreased significantly after the year 2000 (4%). Of these, although 10 of 27 patients survived for 2 years, only 1 continued as a long-term survivor.

There was a patient who had metastatic nodal disease only around the superior mesenteric artery (3 in number, jumping metastasis).[10] The patient was a 59-year-old woman with CaGB with invasion of the hepatoduodenal ligament. She underwent pylorus-preserving pancreatoduodenectomy and adjuvant chemotherapy with S1 and was alive for 61 months after surgery with liver metastasis.

Discussion

In this study the outcome of patients in the N13e group (positive level 13a LN) was clearly equivalent to those in the N1 group. No difference was identified in multivariate analysis for OS. Especially in patients with T1 and T2 disease with positive N13a nodes, good results were obtained by surgical treatment. In this study we have discussed and clarified the surgical outcomes depending on LN metastasis evaluated according to the AJCC eighth edition classification using multivariate analysis. We have considered the cohort in detail.[8,11]

AJCC seventh and eighth editions do not mention the nodal location and status of superior retro-pancreatic (level 13a) LNs in CaGB. The Japanese Society of Biliary Surgery classifies it as N2. Thus the exact status remains unresolved. Behari and Kapoor[6] recently stratified the prognosis of LN metastasis in CaGB and have proposed that peripancreatic, common hepatic artery LNs be considered as N2, whereas superior mesenteric artery, celiac artery LNs be considered as distant metastases along with periaortic nodes. A recent article by Sakata et al[4] corroborates our view.[1,5,6] Therefore we think that nodal location is relevant for defining whether the node is regional or not. We propose that among regional nodes, number is prognostic as per the AJCC eighth edition and that level 13a should be considered to be a regional LN.

CaGB is a complex disease. With various prognostic factors at play, there are no clear-cut answers. Our survival results are consistent with the new AJCC classification, with patients who have 4 or more positive regional LNs faring worse than those with 1–3 regional LNs. However, in our study the prognosis of patients with CaGB with T1/T2 disease with positive level 13a node (total LNs 1–3) was similar to that of patients with N1 disease.

The prognosis was poor in patients with lymph node–positive T3 and T4 disease. Chijiiwa et al[5] have stated that prognosis in CaGB falls sharply in patients with T3/T4 disease. Patients with N2 disease ($\geq$4 positive regional nodes) or positive superior mesenteric artery or para-aortic nodes had a poor prognosis. However, there were occasional long-term survivors among patients who had positive para-aortic nodes. These patients had undergone PD with R0 resection.

The present study with 37 patients with CaGB with positive level 13a LN as the highest level, in the absence of distant metastasis, is the largest reported in the literature. There are few studies in
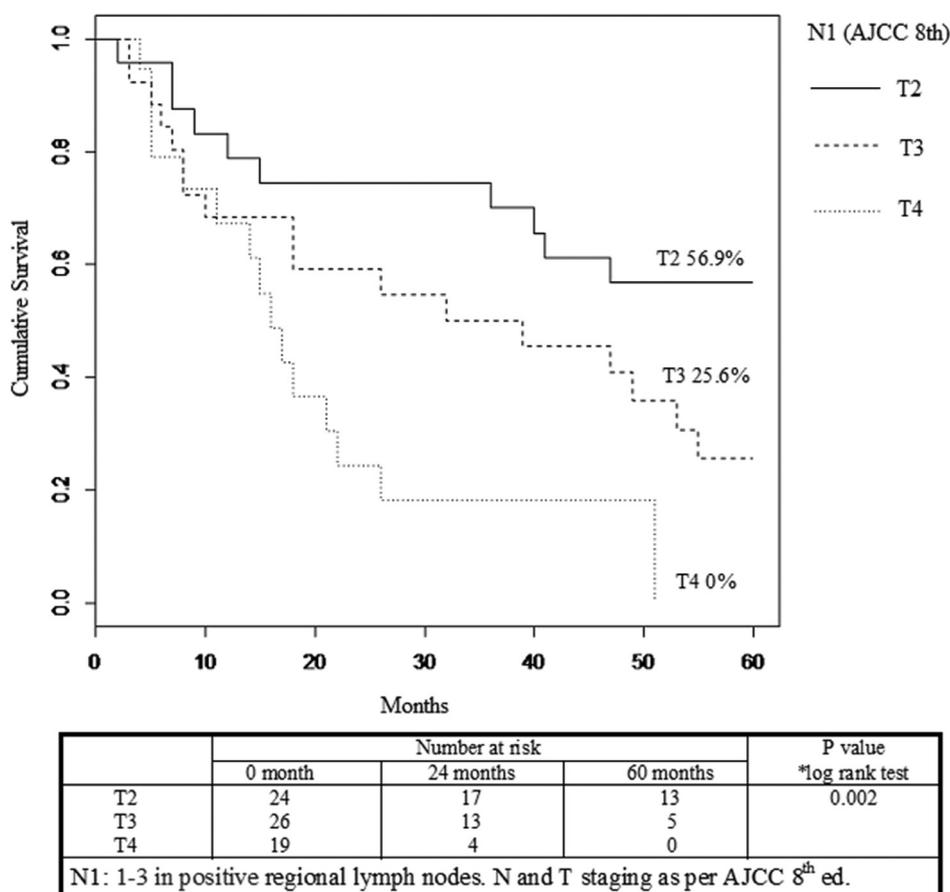
Fig. 3. Overall survival rates in patients with N1 node-positive gallbladder cancer (1–3 nodes in regional LNs), by T stage. *AJCC,* American Joint Committee on Cancer.

the literature that have addressed this particular level.[4,5,12] Shimada et al. have emphasized that the 2 lymph pathways from the gallbladder communicate at the LNs around the pancreatic head. They have reported that the dissection of posterior pancreaticoduodenal LNs results in minor morbidity and mortality and is necessary to improve the prognosis of patients with CaGB with T2 disease.[10]

Ishihara et al,[12] in their analysis of patients in the biliary tract registry in Japan, stated that a positive level 13a LN did not worsen the prognosis of patients with CaGB with otherwise regional node metastasis. Sakata et al[4] found that the 5-year OS of patients with CaGB with positive 13a LN was 31.6% and was similar to that of patients with regional LNs. Chijiiwa et al[5] have stated that these nodes be included as N1 because patients in whom these nodes were positive had a similar survival to those with hepatoduodenal ligament nodes and had better survival than those with more distant nodes. Our findings were similar (Tables 1 and 2).

The cumulative 5-year survival of N1 patients was 32.9% in our study, compared with Onoyama et al[13] (N1, LN metastasis in the cystic duct or pericholedochal, 60%; N2, LN metastasis in the posterosuperior pancreaticoduodenal and common hepatic artery areas, 28.6%), Wakabayashi et al[14] (41.9%), and Chijiiwa et al[5] (N1, cystic duct or pericholedochal LN metastasis 28%). In these reports, because the classification was different, the survival rate in patients with LN metastasis of only the cystic duct or pericholedochal nodes may be better than our results.

The level 13a node behaves like a regional LN in patients with T1 and T2 disease when the total number of LNs are 1 to 3. Eight of 12 of these patients are still alive without recurrence. The prognosis of patients decreased sharply when there were 4 or more total positive LNs, with a less than 10% 5-year survival (mean, 18

months). Long-term survival was associated with T2 disease and N1 or level 13a LN.

Sasaki et al[15] previously stated the benefit of LN clearance associated with PD. It has been found that a greater total LN clearance is associated with a better outcome.[16] All long-term survivors with para-aortic nodes had undergone PD. It would imply that all these patients underwent PD for regional clearance of suspected infiltrating positive regional or level 13a nodes. PD may facilitate greater clearance of nodes that were positive for tumor cells in the final histopathologic determination. Occasionally patients with positive para-aortic LNs survived. The number of patients were too few to draw any conclusion. The surgical strategy followed for surgery for CaGB entails an intraoperative sampling of the interaortocaval nodes.[17] Surgery is abandoned if these nodes are positive for tumor cells on frozen section.

Patients with para-aortic nodes may be suitable candidates for neoadjuvant chemotherapy.[18,19] Creasy et al[20] recently reported on this strategy and have recommended evaluation of neoadjuvant chemotherapy in node-positive CaGB in prospective clinical trials. There have been occasional reports of long-term survival in patients with CaGB with para-aortic LN metastasis.[21]

Major HPD for node-positive CaGB was associated with poor survival in our study. The indications of major hepatectomy alone for CaGB are more standardized and are not discussed here except to say that surgery should not be deferred if the disease has not spread beyond the 13a LN.

PD resulted in the best outcome when it was performed for LN clearance in T2 disease. In patients with T3 and T4 disease with greater nodal burden (N2), we should avoid aggressive resections. It is an interesting prospect that if N2 disease (≥4 regional nodes) is confirmed on intraoperative frozen section biopsy specimens,

Table 2
Univariate and multivariate analysis for overall survival of prognosticators in patients in different nodal groups.

Factor	Group	n	Overall survival 2 y	5 y	P	Hazard ratio (95% CI)	P
N	N13e	26	44.7	40.2	.027	1.0	
	N1	69	55.6	32.9		0.88 (0.47–1.62)	.68
	N13adv or N2	23	31.8	13.3		1.49 (0.73–3.04)	.28
	N14	30	22.6	18.9		0.99 (0.49–1.99)	.98
Age	≥75	116	43.9	31.6	.22		
	<75	32	41.0	19.0			
Women	No	62	43.3	20.9	.11		
	Yes	86	43.2	33.9			
Period	Before 2000	74	37.8	28.9	.32		
	After 2000	74	48.7	27.8			
Preoperative biliary obstruction	without	103	50.1	35.8	.009	1.0	
	with	45	24.8	8.26		1.33 (0.84–2.11)	.22
Hepatectomy	Liver bed	39	46.2	32.6	.27		
	Cholecystectomy	31	47.4	34.5			
	S4aS5	39	48.3	34.1			
	>2 sections	39	31.6	11.5			
BDR or PD	Without	33	47.2	33.7	.74		
	BDR	60	43.7	16.9			
	PD	55	40.2	34.4			
Vascular resection	Without	123	47.1	32.8	.003	1.0	
	With	25	23.5	7.06		1.04 (0.57–1.90)	.90
Blood loss	≤1,500	84	54.5	38.5	<.001	1.0	
	>1,500	64	28.3	16.0		1.58 (1.03–2.43)	.037
Surgery time	≤360	79	46.7	33.3	.23		
	>360	69	39.1	23.0			
Clavien-Dindo classification	<2	87	51.2	36.6	.011	1.0	
	≥3		32.8	18.5		1.48 (0.97–2.24)	.066
R	R0	100	53.9	35.7	<.001	1.0	
	R1	48	18.2	12.1		1.87 (1.17–2.99)	.009
Histology	Pap	30	56.3	48.8	.015	1.0	
	G1/G2	65	51.7	25.5		0.57 (0.29–1.12)	.10
	G3/G4	53	25.1	20.3		1.21 (0.60–2.45)	.59
AJCC 8th	T2	41	72.8	59.8	<.001	1.0	
	T3	63	42.9	21.3		1.58 (0.79–3.18)	.20
	T4	44	13.4	5.37		3.44 (1.54–7.70)	.003
Adjuvant chemotherapy	Absent	119	41.8	27.5	.23		
	Present	29	48.2	33.4			

CI, confidence interval; G1, well differentiated; G2, moderate differentiated; G3, poorly differentiated: G4, undifferentiated; Papillary, ***.

Table 3
Distribution and 5-year survivors (after pancreatico-duodenectomy).

	N1	N13e	N13adv	N2	N14
T2	5 (4)*	5 (4)	1 (1)	0	1 (1)
T3	4 (3)	1 (0)	4 (0)	3 (0)	10 (4)
T4	3 (0)	3 (1)	2 (0)	1 (0)	12 (0)

* The number in parenthesis represents the number of 5-year survivors.

tic modalities, perioperative management, surgical techniques and devices, and adjuvant therapies, have changed over this period.

In conclusion, the survival of patients with CaGB with positive level 13a node (1–3 total positive nodes) is similar to N1 disease, with worsening survival in greater T stages. Thus the retro-pancreatic 13a LN behaves like a regional LN and should be treated as such. It should be a part of standard LN dissection for CaGB. Performance of PD had the best outcome when it was performed for LN clearance in T2 disease. In patients with T3 and T4 disease with greater nodal burden (N2), we should avoid aggressive resections.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.09.003.

proposed major hepatectomies or PD should be deferred. This is not our current practice, but our data seem to suggest that this approach can be evaluated further.

In T2 disease, aggressive resection can be attempted if regional nodes are involved, including N13. Even PD can be performed if it is necessary for nodal clearance. The literature states that regional LN dissection offers long-term survival in selected patients with multiple positive nodes provided R0 resection is feasible.[22]

Adjuvant chemotherapy was administered inconsistently because this study covers data over a long period. It was not a prognostic factor for OS in multivariate analysis in this study (Table 1).

Our study has several limitations. First, it is a retrospective analysis of a prospectively maintained database spanning more than 4 decades. Patient management protocols, including diagnos-

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