

# Our Rationale of Initiating Neoadjuvant Chemotherapy for Hilar Cholangiocarcinoma: A Proposal of Criteria for “Borderline Resectable” in the Field of Surgery for Hilar Cholangiocarcinoma

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## Abstract

**Background** The concept of “borderline resectable” was recently introduced to the field of surgery for pancreatic cancer, and surgical outcomes for this disease with extremely dismal prognosis have improved since the introduction of this concept. However, no such concept has yet been introduced to the field of surgery for hilar cholangiocarcinoma (HCca).

**Aim** To determine a definition and criteria for “borderline resectable” in the field of surgery for HCca.

**Patients and methods** Retrospective analysis of 88 patients undergoing curative-intent surgery for HCca at our institution between May 1992 and December 2008 to clarify independent prognostic factors.

**Results** Survival outcomes were obtained for these 88 patients, with a 5-year overall survival rate of 31.8%. Independent factors predictive of cancer death were determined by multivariate analysis to be the presence of regional lymph node metastasis (LNM) and pathological confirmed vascular invasion (VI). Cumulative survival rates of 23 patients with both LNM and VI who underwent surgery were significantly worse than those of the remaining 65 surgically treated patients and similar to those of 26 patients who were considered to have unresectable disease and treated with non-surgical multidisciplinary treatment during the same study period.

**Conclusion** Outcomes of surgery for cases of HCca showing regional LNM and VI were no better than those of non-surgical treatment for unresectable disease. Coexistence of these two factors indicates oncologically dismal condition and thus such cases should be considered “borderline resectable.” Treatments additional to surgery are required for “borderline resectable” cases to obtain better outcomes.

## Introduction

At present, only surgical extirpation can provide the chance of cure in patients with hilar cholangiocarcinoma (HCca) [1–3]. Nonetheless, HCca has already progressed to unresectable disease at initial presentation in many cases [1–3]. Aggressive surgical procedures including combined

vascular resection and reconstruction were thus introduced soon after the dawn of surgery for this condition [4, 5], achieving resectability in many cases that would have been considered unresectable in the earlier era and bringing about improvements in surgery outcomes [1–3, 6–13]. However, long-term outcomes of surgery for HCca cannot be considered to have reached satisfactory levels, because 5-year patient survival rates after surgery of 30–40% have been reported from world-famous, high-volume centers [7–9, 14–18]. In many cases with HCca, the disease often recurs even after R0 resection [1–5].

On the other hand, in the field of surgery for pancreatic ductal adenocarcinoma (PDAC), the concept of

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“borderline resectable (BR)” was recently introduced, and induction of neoadjuvant treatment for these “BR” cases has been gaining wider acceptance and showing improved long-term outcomes [19–21]. Rather than HCca, PDAC has gained notoriety as a disease showing an extremely dismal prognosis, with most patients dead within a few years, at least until recently [19–21]. Although clear and definitive definitions and criteria for “BR” lacked initially, the concept of “BR” can be said to have been contributing to the improved outcomes of surgery for PDAC [19–21]. Consequently, the current National Comprehensive Cancer Network (NCCN) guideline for PDAC clearly indicates the anatomical criteria for resectability based on the radiological findings [22]. A rough definition of “BR” can be described as follows: Those cases for which surgery is likely to result in R1 resection, long-term outcomes after surgery are not markedly different from the outcomes of cases treated non-surgically [19–21]. Namely, the term “BR” implies “oncologically challenging” rather than “technically challenging.” The term “BR” itself was already used in the field of surgery for HCca in the study of Choi et al. [23]. However, they referred only to the longitudinal extent of the disease, i.e., curative-intent surgery is likely to result in R1/2 resection by positive ductal margin status in cases of the “BR” HCca they defined. However, significance of positive ductal margin status has been controversial in surgery for HCca. Several reports demonstrated that positive ductal margin status did not affect postoperative survival [24–26]. Therefore, the term “BR” used in the Choi’s study might not directly indicate the oncological dismalness.

In 2009, we started a program of neoadjuvant chemotherapy (NAC) for selected cases of HCca, although our institution obtained long-term outcomes of surgery for HCca equivalent with the above-stated outcomes reported from world-famous, high-volume centers up to 2008. By 2008, the 5-year patient survival rate was 31.8% among 88 patients with HCca undergoing curative-intent surgery at our institution. In the monograph, we showed our rationale for applying NAC to selected cases of HCca; that is, we proposed criteria for “BR” in surgery for HCca. We consider that the term “BR” should indicate “oncologically dismal condition.” For this purpose, we investigated clinicopathological variables in 88 patients with HCca receiving curative-intent surgery up to 2008 in our institution, to elucidate independent factors predictive of death.

## Patients and methods

### Patients and preoperative workup

Between May 1992 and December 2008, 129 patients with HCca were treated at our institution. Of these 129 patients, 88 patients underwent curative-intent surgery, with a resection rate of 68.2%.

Ultrasonography and computed tomography were used in all patients for preoperative tumor staging. Preoperative jaundice was mitigated by endoscopic and/or transhepatic biliary drainage if present. Location and extension of tumors were classified according to the Bismuth–Corlette classification [27]. If regional lymph node metastasis and/or distant metastasis were suspected, 18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) was performed.

### Operative procedures

The following types of hepatectomy were selected according to the tumor and patient condition: right tri-sectionectomy; right hemi-hepatectomy; left tri-sectionectomy; left hemi-hepatectomy; and central bi-sectionectomy. Caudate lobectomy and resection of the extrahepatic bile duct were always included in all types of hepatectomy. If tumor extension reached the lower bile duct in the pancreatic head, hepatopancreatoduodenectomy (HPD) was performed. If the estimated resection volume of the liver exceeded 60% of total liver volume, portal vein embolization (PVE) for the planned resected part of the liver was performed 3 weeks before surgery. We routinely perform sampling of retropancreatic para-aortic lymph nodes located between aorta and inferior vena cava. During this study period, no standard chemotherapeutic regimen for cholangiocarcinoma existed. Therefore, we included the following patients into candidates for curative-intent surgery: i.e., patients with para-aortic lymph node metastasis confined to the retropancreatic region between aorta and inferior vena. Thus, para-aortic lymph node dissection was performed for such patients unless the patient had other distant metastasis. All 88 patients routinely underwent lymph node dissection around the peri-pancreatic area and hepatoduodenal ligament, and the para-aortic node dissection as stated above was performed for 18 of the 88 patients. When invasion of the hepatic artery and/or portal vein that fed the future liver remnant was suspected, vascular resection and reconstruction were performed. Intraoperative frozen section diagnosis of the proximal and/or distal ductal margin was performed as occasion allowed. If a positive ductal margin proved on frozen section, additional resection of the bile duct was performed as far as

surgically possible. When metastasis of para-aortic lymph node, liver, and/or peritoneum was diagnosed intraoperatively, surgery was abandoned unless these lesions were surgically and reasonably removable.

### Clinicopathological investigations

Clinicopathological variables were retrospectively obtained from the medical records and reviewed. Resection status and tumor stage were determined according to the American Joint Committee on Cancer (AJCC) classification [28].

### Follow-up protocol after surgery

All patients attended regular outpatient clinics at 4-week intervals and received tumor marker checkups at 4-week intervals and computed tomography at 12-week intervals up to 5 years after surgery. Survival was measured from the date of surgery. Follow-up was continued until December 31, 2016 or death.

### Statistical analysis

The Chi-square test and Fisher's exact test were used for categorical variables. Numerical variables were analyzed by the Mann–Whitney *U* test. Survival was assessed by Kaplan–Meier life table analysis with Breslow–Gehan–Wilcoxon test. For multivariate analysis, variables found to be significant in univariate analyses and/or considered important on the basis of logical and/or biomedical grounds were entered into the Cox proportional hazards model to identify factors independently associated with survival by the forced-entry or backward-elimination manner, as appropriate. Results are shown as the percentage of patients or as the median (range). SPSS Statistics for Windows version 22 software (IBM Corporation, Armonk, NY) was used, and two-tailed *P*-values less than 0.05 were considered significant.

## Results

### Clinical characteristics

Intraoperative variables are summarized in Table 1. Twenty-four of the 88 patients underwent limited resection other than major hepatectomy because of insufficient hepatic reserve. Combined portal vein resection and reconstruction were performed for 29 patients (32.9%), and hepatic artery resection and reconstruction were performed for 22 patients (25.0%). HPD was performed in eight patients (9.1%).

**Table 1** Surgical procedure and short-term outcomes in 88 this study cohorts

Variables	
Type of procedure	
EBDR*	15 (with PVR <sup>†</sup> , 1; with HAR <sup>‡</sup> , 1; with PD <sup>§</sup> , 8)
Hepatectomy	
S1, 5, 6, 7, 8	18 (with PVR <sup>†</sup> , 7; with HAR <sup>‡</sup> , 1; with PD <sup>§</sup> , 2)
S1, 2, 3, 4, 5, 8	9 (7; 6; 0)
S1, 2, 3, 4	35 (11; 11; 4)
S1, 4, 5, 8	2 (1; 2; 0)
S1, 4	3 (1; 1; 1)
S1, 5, 8	2 (0; 0; 0)
S1	4 (1; 0; 1)
Total	88 {PVR <sup>†</sup> , 29 (33%); HAR <sup>‡</sup> , 22 (25%); PD <sup>§</sup> , 16 (18%)}
Mean operating time (range)	792 min (480–1155 min)
Mean blood loss (range)	2813 ml (400–12700 ml)
Patients necessitating intraoperative transfusion	59 (67.0%)
90-day mortality	5 (5.6%)
Decisive complications for mortality	
Liver failure caused by excessive resected liver	2
Portal vein thrombosis	2
Ruptured pseudoaneurysm	1

\*Extended bile duct resection

<sup>†</sup>Portal vein resection and reconstruction

<sup>‡</sup>Hepatic arterial resection and reconstruction

<sup>§</sup>Pancreaticoduodenectomy

Sixty-eight patients (77.2%) suffered from postoperative complications. Anastomotic leakage of hepaticojejunostomy was most common, seen in 19 patients (21.5%). Other complications included intraabdominal abscess in 16 patients (18.1%), bile leakage from the liver cut surface in 16 patients (18.1%), respiratory failure in 12 patients (13.6%), liver failure in nine patients (10.2%), cholangitis in nine patients (10.2%), pancreatic fistula in 5 patients (5.6%), liver abscess in 5 patients (5.6%), hemoperitoneum requiring re-celiotomy in 4 patients (4.5%), portal vein thrombosis in three patients (3.4%), and hepatic artery thrombosis in two patients (2.2%). As a result, major complications defined as complications of Clavien–Dindo [29] grade III or higher were observed in 58 patients (65.9%). Mortality within postoperative 90 days was seen in five of the 88 patients (5.6%).

### Pathological findings

Histological differentiation of tumors was well in 33 patients (37.5%), moderate in 41 (46.5%), and poor in 14

(15.9%). Perineural invasion and hepatic parenchymal invasion were identified in 62 patients (70.4%) and 44 patients (50.0%), respectively. Invasion of the portal vein and hepatic artery was identified in 33 patients (37.5%) and 16 patients (18.1%), respectively. Of these, 13 patients showed invasion of both the hepatic artery and portal vein. As a result, 36 of the 88 patients (40.9%) displayed pathologically proven vascular invasion (VI) involving the hepatic artery and/or portal vein. Forty-six patients (52.2%) showed lymph node metastasis (LNM). Eighteen patients (20.4%) had a positive ductal margin, and 16 patients (18.1%) had a positive radial margin. Distant lymph node metastasis, i.e., extra-regional nodes including lymph nodes neighboring the para-aortic, peri-pancreatic, and common hepatic artery areas, was diagnosed in 21 patients (23.8%). Five patients showed solitary metastatic foci in the resected liver. As a result, 22 patients corresponded to M1. (Four patients showed both distant lymph node and liver metastases.) R0 resection was performed in 60 patients (68.1%), R1 in 25 patients (28.4%) and R2 in 3 patients (3.4%). Regarding three patients resulting in R2 resection, macroscopic proximal ductal margin status was considered obviously positive. However, subsequent reconstructability could not be guaranteed if additional resection was performed. Thus, these three patients resulted in R2 resection. As to the AJCC 7th classification [28], two patients (2.2%) corresponded to pathological stage 0, three patients (3.4%) to stage I, 19 patients (21.5%) to stage II, four patients (4.5%) to stage IIIA, 12 patients (13.6%) to stage IIIB, 26 patients (29.5%) to stage IVA, and 22 patients (25.0%) to stage IVB.

### Overall survival and prognostic factors

Median follow-up was 54.4 months. Fifty-six patients died of the disease, and 12 patients died of other causes without evidence of recurrence. Sites of recurrent disease are summarized in Table 2. Although majority of patients with recurrent disease received chemotherapy, gemcitabine-based chemotherapy was administered to only four of these patients because the Japanese social insurance coverage of gemcitabine for biliary tract cancer was approved in 2006. Accordingly, because the standard chemotherapeutic regimen did not exist at that time, surgical resection was attempted for the following sites of the recurrence: lung in one patient, percutaneous biliary drainage tract in one, and para-aortic lymph node in one. Overall survival rates for the 88 patients who underwent surgery were 73.9% at 1 year, 45.5% at 3 years, and 31.8% at 5 years (median survival time 32.0 months). Twenty-eight patients survived for more than 5 years after surgery. During the same study period, 41 patients were treated non-surgically because of unresectable disease. Of these, 15 patients received best

**Table 2** Site of recurrent disease

	<i>n</i> = 88	(%)
Recurrence (%)	61	(69.3)
Site of recurrence		
Local	14	(15.9)
Lymph node	12	(13.6)
Liver	9	(10.2)
Peritoneum	24	(27.2)
Lung	10	(11.3)
PTCD tract	2	(2.3)
Brain	2	(2.3)
Bone	3	(3.4)

PTCD percutaneous transhepatic cholangio drainage

supportive care (BSC) only and the other 26 patients received multidisciplinary treatment (MDT) including chemotherapy, radiotherapy, and biliary drainage. The 1-year survival rate for these 41 patients was 39.0%, and the median survival time was 9.1 months. The survival outcome was thus significantly better in the 88 patients who underwent surgery than in the 41 patients treated non-surgically ( $P < 0.001$ ).

Prognostic factors determined by univariate analysis were serum concentration of carbohydrate antigen (CA)19-9 ( $P = 0.015$ ), Bismuth–Corlette classification ( $P = 0.018$ ), vascular resection and reconstruction ( $P = 0.027$ ), postoperative morbidity ( $P = 0.044$ ), perineural invasion ( $P = 0.008$ ), VI ( $P = 0.012$ ), LNM ( $P < 0.001$ ), excisional margin status ( $P < 0.001$ ), R status (R0, R1, or R2) ( $P < 0.001$ ), AJCC pT factor ( $P = 0.005$ ), and AJCC TNM stage ( $P < 0.001$ ). Tumor differentiation ( $P = 0.142$ ), hepatic parenchymal invasion ( $P = 0.148$ ), and cut-end margin status of bile duct ( $P = 0.113$ ) did not affect survival (Table 3).

Multivariate analysis demonstrated that factors independently predictive of mortality were the presence of LNM (hazard ratio (HR), 2.764; 95% confidence interval (95% CI), 1.687–4.528) and VI (HR 1.755; 95% CI 1.089–2.828) (Table 3).

### Impact of lymph node metastasis (LNM) and vascular invasion (VI)

The 5-year survival rate was significantly worse in patients receiving surgery with LNM than in those without (15.2% vs 50.0%;  $P < 0.001$ ) (Fig. 1a). However, the 5-year survival rate of patients with LNM was significantly better than that of the 41 patients treated non-surgically ( $P < 0.001$ ) (Fig. 1a). Furthermore, 5-year survival rates were significantly worse in patients who underwent surgery with VI than in those without VI (19.4% vs. 40.4%;

**Table 3** Results of univariate and multivariate analyses for prognostic factors for overall survival

Factors	Univariate analysis				Multivariate analysis	
	No. of patients	5-year survival rate (%)	Median survival time (month)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
<i>Patients characteristics</i>						
Gender						
Male	62	30.6	33.8	0.821		
Female	26	34.6	25.0			
Age (years)						
<67	43	32.6	33.8	0.438		
≥67	45	31.1	30.4			
CA19-9 (IU/ml)						
<37	27	55.6	71.9	0.015		0.230
≥37	61	21.3	25.0			
Preoperative jaundice						
Absent	56	35.7	32.4	0.179		
Present	32	25.0	21.7			
Bithmuth–Corlette classification						
Type I, II, or III	58	41.4	36.5	0.018		0.296
Type IV	30	13.3	25.9			
<i>Perioperative factors</i>						
Preoperative PVE <sup>‡</sup>						
Not done	63	41.4	36.5	0.018		
Done	25	13.3	25.9			
Major hepatectomy						
Not done	26	38.5	39.3	0.221		
Done	62	29.0	27.1			
VRR <sup>§</sup>						
Not done	51	39.2	32.4	0.027		
Done	37	21.6	29.8			
Postoperative morbidity						
Absent	30	43.3	37.8	0.044		0.296
Present	58	25.9	25.9			
<i>Pathological factors</i>						
Tumor differentiation						
Well	33	42.4	39.0	0.142		
Others	55	25.5	27.1			
Perineural invasion						
Absent	26	50.0	50.0	0.008		0.989
Present	62	24.2	27.1			
Hepatic parenchymal invasion						
Absent	44	40.9	38.1	0.148		
Present	44	22.7	24.9			
Vascular invasion						
Absent	52	40.4	38.1	0.012	1.755(1.089–2.828)	0.021
Present	36	19.4	21.7			
Lymph node metastasis						
Absent	42	50.0	50.0	<0.001	2.764(1.687–4.528)	<0.001
Present	46	15.2	19.0			
Excisional margin of tumor						
Negative	72	37.5	36.8	<0.001		

**Table 3** continued

Factors	Univariate analysis			Multivariate analysis	
	No. of patients	5-year survival rate (%)	Median survival time (month)	<i>P</i> value	Hazard ratio (95% CI) <i>P</i> value
Positive	16	6.3	9.9		
Cut end margin of bile duct					
Negative	70	34.3	32.4	0.113	
Positive	18	22.2	27.1		
Residual tumor					
R0	60	40.0	37.8	<0.001	
R1 or R2	28	14.3	13.3		
AJCC <sup>¶</sup> T factor					
Tis or T1	5	80.0	N.R.	0.005	
T2a	24	41.7	36.8		
T2b	10	50.0	50.0		
T3	11	27.3	17.5		
T4	38	15.8	25.0		
AJCC stage					
0 or I	5	80.0	N.R.	<0.001	
II	19	47.4	50.0		
IIIA	4	75.0	N.R.		
IIIB	12	41.7	34.4		
IVA	26	19.2	29.8		
IVB	22	9.1	12.5		

\*5-year over all survival rate

†Median survival time

‡Portal vein embolization

§Vascular resection and reconstruction

¶American Joint Committee on Cancer

$P = 0.012$ ) (Fig. 1b), whereas the 5-year survival rate of patients with VI was significantly better than that of the 41 patients treated non-surgically ( $P < 0.001$ ) (Fig. 1b).

### Criteria for “borderline resectable”

A comparison of cumulative survival rates among the following patient groups is shown in Fig. 1c: patients without LNM or VI ( $n = 29$ ); patients with either LNM or

VI ( $n = 36$ ); patients with both LNM and VI ( $n = 23$ ); patients treated with non-surgical MDT ( $n = 26$ ); and patients who received only BSC ( $n = 15$ ). The 5-year survival rate of patients without LNM or VI was better than that of patients with either LNM or VI (51.7% vs 33.3%,  $P = 0.009$ ). However, 5-year survival rates were significantly better in patients with either LNM or VI than in patients with both LNM and VI or in patients who received non-surgical MDT. The R0 resection rate of the 23 patients

**Fig. 1** Comparison of postoperative survival among patient groups divided by accompanying independent factors. **a** Comparison of cumulative survival rate among patients undergoing surgery with and without lymph node metastasis and patients treated non-surgically. Cumulative postoperative survival rate of patients undergoing surgery without lymph node metastasis ( $n = 42$ ) was significantly better than that of patients undergoing surgery with lymph node metastasis ( $n = 46$ ). However, cumulative postoperative survival rate of the latter was significantly better than cumulative survival rate after the diagnosis of patients treated non-surgically ( $n = 41$ ). **b** Cumulative postoperative survival rate of patients undergoing surgery with pathologically confirmed vascular invasion ( $n = 36$ ) was significantly worse than that of patients undergoing surgery with negative vascular

invasion ( $n = 52$ ). **c** Comparison of cumulative survival rate among the following patient groups: patients undergoing surgery without lymph node metastasis (LN) or histological vascular invasion (VI), patients undergoing surgery either with LN or VI, patients undergoing surgery both with LN and VI, patients receiving non-surgical multidisciplinary treatment, and patients only receiving best supportive care. Cumulative postoperative survival rate of patients undergoing surgery both with lymph node metastasis (LN) and histological vascular invasion (VI) was significantly worse than other groups of patients undergoing surgery. Furthermore, cumulative postoperative survival rate of patients undergoing surgery both with LN and VI was no better than cumulative survival rate after the diagnosis of patients treated by non-surgical multidisciplinary treatment

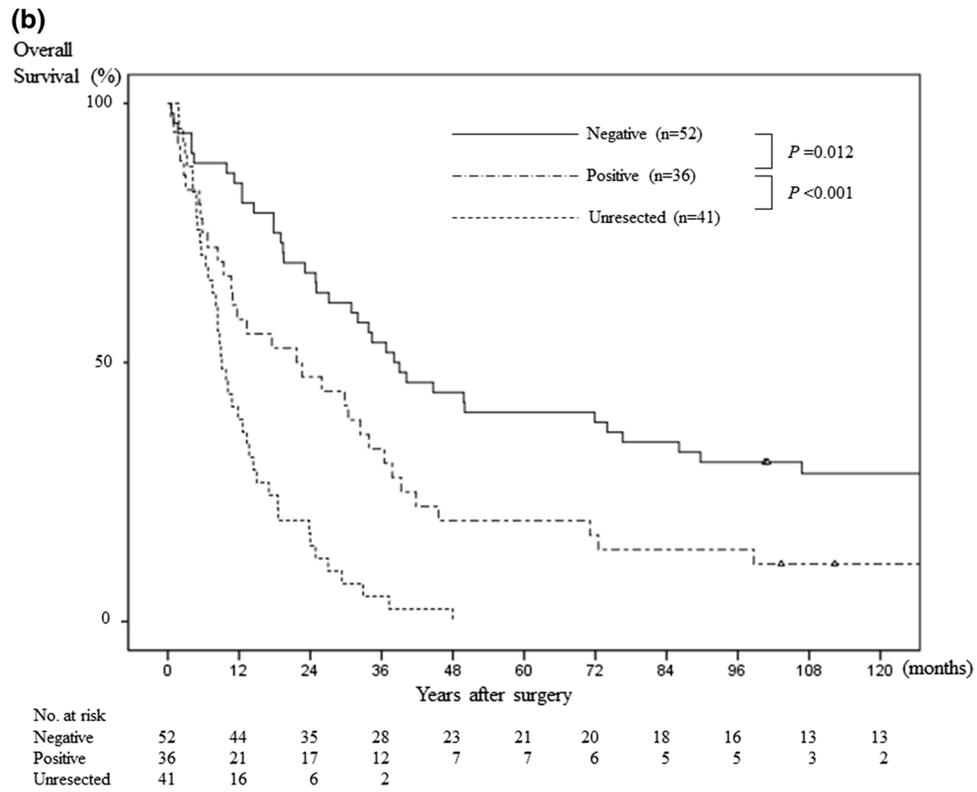
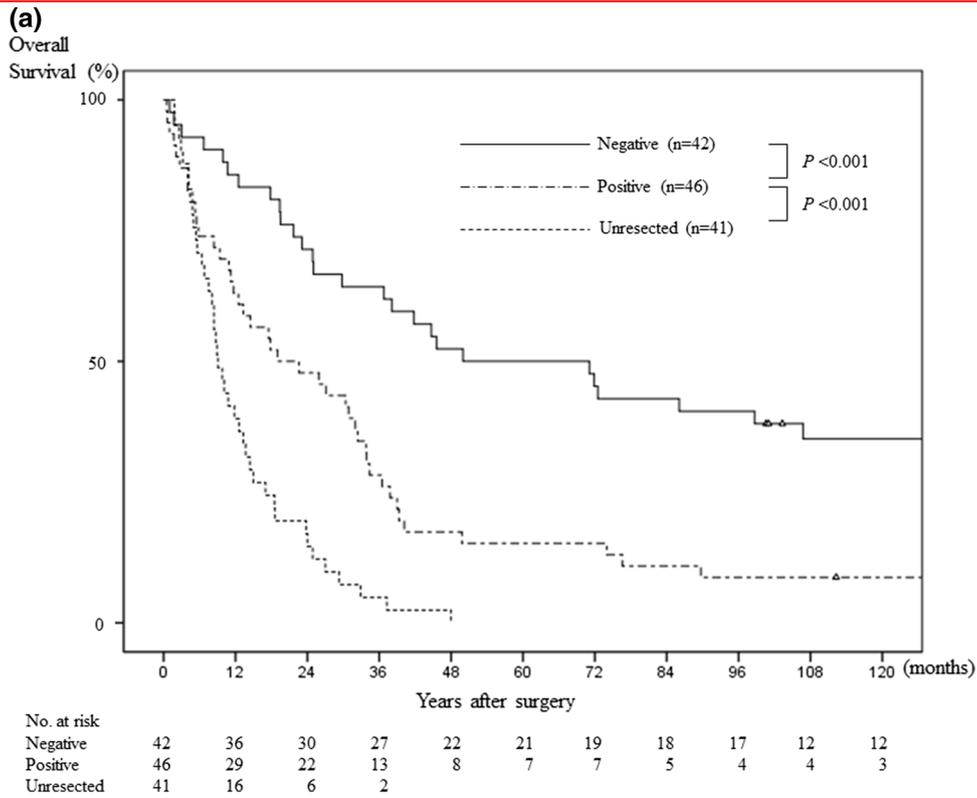
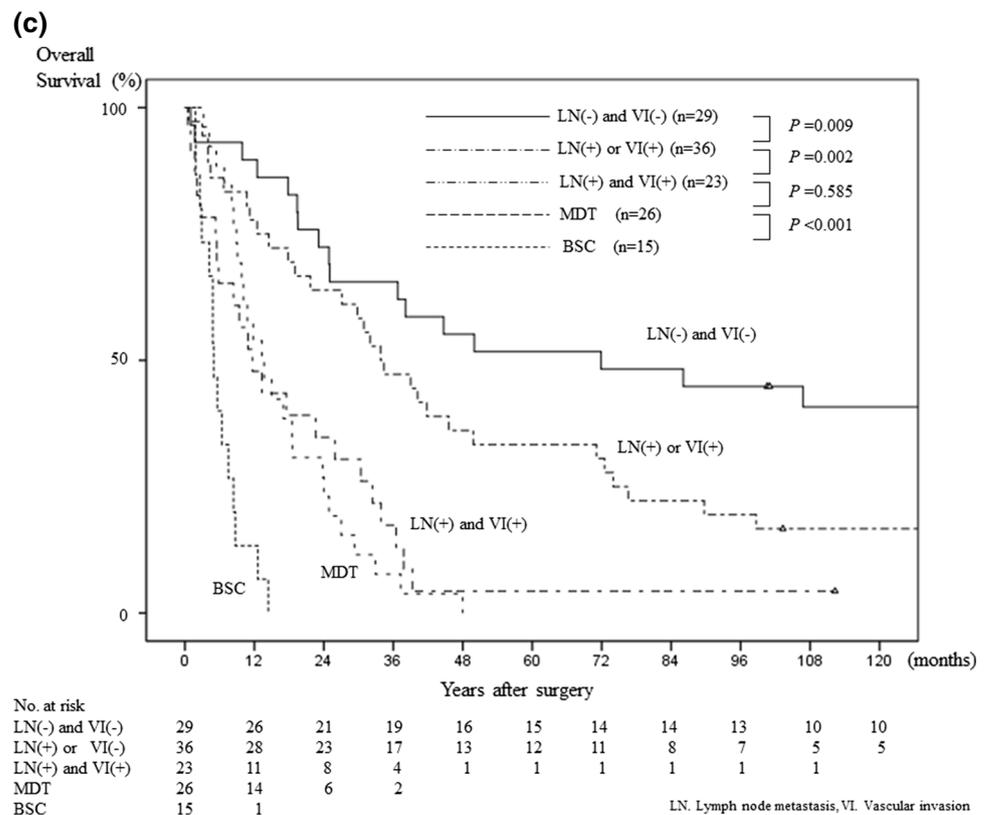


Fig. 1 continued



with both LNM and VI was 52.1%, worse than the 73.8% seen in the other 65 patients who underwent surgery with marginal significance ( $P = 0.055$ ). Furthermore, the 5-year survival rate of patients with both LNM and VI showed no difference from that of patients who received non-surgical MDT ( $P = 0.585$ ) (Fig. 1c). In other words, the effect of surgery was no better than non-surgical MDT in this population. Cases with both lymph node metastasis and vascular invasion should thus be considered “BR” in terms of the fact that only dismal outcomes were brought on by surgery-alone strategy in such cases (Fig. 2).

## Discussion

In the field of surgery for PDAC, the concept of “BR” and a strategy of surgery with neoadjuvant and/or adjuvant treatment for such “BR” cases have been proposed and are gaining wider acceptance [19–21]. As the current NCCN guideline for PDAC clearly indicates the anatomical criteria for “BR” [22], this concept can be addressed as a milestone toward improving outcomes of surgery for PDAC [19–21].

With the increased surgeons’ experiences and technical refinements, safety (that is, the short-term outcomes of aggressive procedures including vascular resection and reconstruction) and the gains in R0 resection rates have certainly improved in the field of surgery for HCca [1–3, 6–18, 27, 30–37]. However, chronological improvements in the reported long-term outcomes of surgery have not been observed [6–18, 27, 30–37]. Namely, surgery alone could cure markedly limited populations with this disease entity even if R0 resection is achieved. Furthermore, HCca surgery often accompanies severe postoperative complications as shown in the present study. Hence, curative-intent surgery, of which survival outcomes are no better than those of non-surgical treatment, should be considered as futile surgery and therefore be avoided as possible. The present study demonstrated LNM and VI as independent predictors of mortality and corroborated that survival outcomes of surgery alone for HCca patients with both LNM and VI were unsatisfactory, with cumulative survival rates similar to those of the patient group treated without surgery. We therefore considered this patient group as “BR,” and in 2009, we commenced a program of NAC for those patients in whom the presence of both regional



**Fig. 2** A representative case of “borderline resectable” cases defined in the present study. This figure shows a case of Bismuth–Corlette IIIa which showed vascular invasion and lymph node metastasis. The tumor invaded the right hepatic artery (white arrow). Furthermore, swelling of several regional lymph nodes in the hepatoduodenal ligament was noticed (white arrowheads). These lymph nodes revealed increased uptake of 18-fluorodeoxyglucose in positron emission tomography/computed tomography imaging. The tumor was removed by right hepatectomy, in which vascular resection and reconstruction were not necessitated. Invasion of right hepatic artery and regional lymph node metastases was pathologically proven in resected specimen in this case although combined vascular resection and reconstruction were not necessitated

LNM and VI was strongly suggested from preoperative diagnostic imaging. In surgery for PDAC, anatomical criteria of resectability are dictated by radiological findings of abutment of lesion to the adjacent major vessels, such as portal vein, superior mesenteric artery, celiac artery, or common hepatic artery [22]: These major vessels must be reconstructed in principle if combined vascular resection is necessitated. In other words, “technically challenging” disease appears directly “oncologically challenging” in surgery for PDAC. On the other hand, major vessel resection without reconstruction can be sometimes carried out in surgery for HCca even if involving major vessels. For example, in cases of Bismuth–Corlette IIIa HCca in which the right hepatic artery and/or right portal vein is involved by the tumor, these major vessels can be resected without reconstruction in some cases of right hepatectomy (Fig. 2). That is, in surgery for HCca, “technically unchallenging” but “oncologically challenging” cases are sometimes encountered. In addition, extent of hepatectomy must be altered according to the hepatic reserve of each case in surgery for HCca. Therefore, selection of operative method depends not only on tumor factors, but also on hepatic reserve in HCca surgery. In other words, resectability cannot be determined by radiological findings alone in HCca surgery unlike PDAC surgery. Considering these issues, we defined the term “BR” as “the oncologically dismal condition even if resected.”

Several reports demonstrated the efficacy of postoperative adjuvant chemotherapy (PAC) for biliary tract cancer (BTC) [38–40]. In fact, we are recognizing PAC as promising strategy and using PAC for patients exhibiting risk factors for the pathological findings of resected specimen such as LNM, VI, or R1 resection, irrespective of whether using NAC or not in our current treatment program. However, some authors reported that gemcitabine-based PAC for patients with BTC who received major hepatectomy was more likely to cause severe toxicity than that for BTC patients receiving surgery other than major hepatectomy [38–40]. Curative-intent surgery for HCca usually requires major hepatectomy. Meanwhile, an R0 resection has been considered essential for favorable outcomes of surgery for HCca. We considered that NAC may neutralize the negative impact of LNM and VI as well as the invasive front of the disease, i.e., the effect of NAC may improve R0 resection rate. That is why we prioritize NAC rather than PAC.

We recognized the fact that the two factors composing criteria for “BR” proposed in the present study were both pathologically confirmed factors as the significant limitation to our NAC policy. To transcend this limitation, we utilized the three-dimensional imaging, incorporating conventional contrast enhancement and drip-infusion-cholangiography, which enables 360° imaging of each vasculature to improve the preoperative diagnostic accuracy of VI since 2003 [41]. With regard to the LNM, we used PET/CT [42, 43]. Although these modalities might have not yet reached the sufficient level of accuracy for VI or LNM, we consider that these modalities are the most promising radiologic modalities for our purpose at present. In addition, efficacy of diffusion MRI for diagnosing LNM [44, 45] has been studied in parallel with that of PET/CT. To improve diagnostic accuracy for LNM and/or VI, we are attempting various combinations of multimodal diagnostic imaging findings. At the same time, whether VI and/or LNM actually existed or not cannot be confirmed from the resected specimen in cases which markedly respond to NAC followed by surgery. Recently, the MD Anderson Cancer Center group reported that chronological change in serum CA19-9 before and after surgery was independently predictive of surgical outcomes for biliary tract cancer [46]. Notably, they demonstrated that the normalization of CA19-9 after NAC led to the favorable outcomes. We considered that combination of radiological findings and biomarkers such as CA19-9 may be more prognosticative than radiological findings alone, especially for cases receiving NAC. Thus, we are currently constructing a prospective database to examine this issue. As such, although we recognized that significant limitations exist to preoperative diagnosis with these pathological factors, we

believe that our NAC policy will be justified by overall improvements in cases treated at our institution.

We could not have determined NAC regimen until recently mainly because the standard chemotherapeutic regimen for BTC did not exist at that time when we initiated the NAC program. In other words, we used gemcitabine-S-1 combination (GS) as the NAC regimen at the beginning of the program because the Japanese social insurance coverage of cisplatin for BTC was not approved [47]. However, soon after we initiated the NAC program, gemcitabine–cisplatin combination (GC) was addressed as the standard first-line chemotherapy for patients with BTC ineligible for surgery in the Japanese clinical guidelines as revised in 2013. Therefore, we must have conducted a pilot study comparing GC used as NAC to GS. This pilot study recently reached the consensus of our institutional cancer board, and we subsequently initiated a prospective study regarding NAC for patients with the “BR” HCCa. At this stage, a benefit of NAC for increasing the resection rate has been realized, and in the near future, we plan to assess the efficacy of NAC for the long-term outcomes of surgery for this patient group. Furthermore, surgical outcomes of HCCa should be considered unsatisfactory even in cases without VI or LNM. If results of our NAC program reveal acceptable tolerability and improvement of surgical outcomes of BR cases we defined, we will expand the indication of NAC toward cases without VI or LNM.

In conclusion, satisfactory long-term outcomes could not be obtained by surgery alone for patients with HCCa fulfilling the following two factors. These two factors included the presence of regional LNM and VI. Cases fulfilling these two factors are of oncological dismalness. Thus, such cases should be considered as “borderline resectable” and provided with additional treatment to surgery in order to obtain better survival outcomes.

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