Hepatectomy With Portal Vein Resection for Hilar Cholangiocarcinoma

Audit of 52 Consecutive Cases

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Objective: To better determine the role of portal vein resection and its effect on survival, as well as to appreciate the impact of portal vein invasion on prognosis in hilar cholangiocarcinoma.

Summary Background Data: Hepatectomy with portal vein resection is sometimes performed for locally advanced hilar cholangiocarcinoma. However, the significance of microscopic invasion of the portal vein has not been determined.

Methods: Medical records of 160 patients with hilar cholangiocarcinoma who underwent macroscopically curative hepatectomy with (n = 52) or without portal vein resection (n = 108) were reviewed. Invasion of the portal vein was assessed histologically on the surgical specimen, and results were correlated with clinicopathologic features and survival.

Results: Surgical mortality, including all hospital deaths, was similar in patients who did and did not undergo portal vein resection (9.6% vs. 9.3%), but the primary tumor was more advanced in patients who underwent portal vein resection. Histologically, no invasion was found in 16 (30.8%) of resected portal veins. However, dense fibrosis adjacent to the portal vein was common, and the mean distance between the leading edge of cancer cells and the adventitia of the portal vein was 437 ± 431 μm. The prognosis was worse in patients with than without portal vein resection (5-year survival, 9.9% vs. 36.8%; $P < 0.0001$). The presence or absence of microscopic invasion of the resected portal vein did not influence survival (16.6 months in patients with microscopic invasion vs. 19.4 months in those without; $P = 0.1506$). Multivariate analysis identified histologic differentiation, lymph node metastasis, and macroscopic portal vein invasion as independent prognostic factors.

Conclusions: Microscopic invasion of the portal vein may be misdiagnosed clinically in patients with hilar cholangiocarcinoma. However, the distance between tumor and adventitia is so narrow that curative resection without portal vein resection is unlikely to be possible. Gross portal vein invasion has a negative impact on survival, and hepatectomy with portal vein resection can offer long-term survival in some patients with advanced hilar cholangiocarcinoma.

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Portal vein invasion was previously a main cause for unresectability of hilar cholangiocarcinoma: several authors have stressed the importance of using portography to demonstrate portal vein invasion as a contraindication to surgery.[1,2] However, this philosophy recently has become outdated. Several authors have described portal vein resection for advanced biliary cancer and have advocated an aggressive surgical strategy.[3–14] We also have performed combined hepatobiliary and portal vein resection in patients with advanced hilar cholangiocarcinoma.[5,8,10,13] In our experience, despite the suggestion of macroscopic portal vein involvement during intraoperative inspection, histologic examination often revealed no cancer in the resected portal vein. No report has addressed in detail the microscopic disease status of the resected portal vein and its predictive power in hilar cholangiocarcinoma. In the present study, we reevaluated the histology of resected portal vein specimens from patients with hilar cholangiocarcinoma who underwent macroscopically curative resection, to elucidate the true status of the resected portal vein and to determine the survival impact of portal vein invasion.

MATERIALS AND METHODS

Patients

Between 1979 and 2000, 240 patients with hilar cholangiocarcinoma were treated at the First Department of Surgery, Nagoya University Hospital. Fifty-two (21.7%) underwent laparotomy and/or biliary drainage alone because they had advanced disease or their general condition was too poor

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to tolerate curative resection. The remaining 188 (78.3%) underwent tumor resection with (n = 174) or without hepatectomy (n = 14). Of the 174 hepatectomized patients, the resection was macroscopically curative in 162, with (n = 54) or without concomitant portal vein resection (n = 108). Of the 54 patients who underwent combined liver and portal vein resection, 2 were excluded from this study because their portal veins were resected, not because of malignant invasion but due to kinking (n = 1)[15] or intraoperative injury (n = 1). Thus, 35 men and 17 women, with a mean age of 60.3 ± 10.6 years (range, 33–80 years), are the subjects of this report.

Of the 52 study patients, 43 (82.7%) were jaundiced on admission with a mean serum total bilirubin concentration of 12.5 ± 7.5 mg/dL (range, 2.1–32.9 mg/dL). Percutaneous transhepatic biliary drainage (PTBD) was performed in 50 (96.2%) patients, including 7 nonjaundiced patients with intrahepatic biliary dilatation as well as the 43 jaundiced patients, to relieve obstructive jaundice, to treat segmental cholangitis,[16] and to display the entire biliary tree for preoperative diagnosis of cancer extent along the separated intrahepatic segmental ducts. The method of PTBD was Takada's direct anterior approach under fluoroscopic control.[17] A total of 121 drainage catheters were placed in the 50 patients, with a mean number of 2.4 ± 1.3 catheters (range, 1–7 catheters) in each patient. Eleven patients underwent single PTBD, while the remaining 39 patients received multiple PTBD.[18,19] Preoperative portal vein embolization was also indicated in 17 (32.7%) patients. This intervention was performed under percutaneous transhepatic approach approximately 2 weeks before hepatectomy.[20,21] Embolized portal vein was the right portal vein in 10 patients, the right portal vein plus left medial portal branch (right trisegment portal vein embolization) in 4, and the right anterior portal branch plus left portal vein (left trisegment portal vein embolization) in 3.

Operative Procedures

All hepatectomies were carried out after serum total bilirubin concentration had decreased <2 mg/dL. Right trisegmentectomy (resection of Couinaud's segment 4–8) was performed in 10 patients, right lobectomy (resection of segment 5–8) in 21, left trisegmentectomy (resection of segment 2–5 and 8) in 5, left lobectomy (resection of segment 2–4) in 14, and other procedures in 2. All patients underwent en bloc resection of the caudate lobe and extrahepatic bile duct. Nine (17.3%) patients also underwent combined pancreatoduodenectomy, and 1 (1.9%) patient underwent hepatic artery resection and reconstruction. Parenchymal transection was carried out using an ultrasonic dissector or Péan forceps according to surgeon's preference, under both the hepatic artery and portal vein clamping for15 minutes at 5-minute intervals. Operation time was 745 ± 161 minutes, and blood loss was 3732 ± 2784 mL.

All portal vein resections were carried out only when the portal vein adhered to and could not be freed from the tumor during skeletonization resection of the hepatoduodenal ligament. Even if invasion were suspected on preoperative portography, the portal vein was not resected when the vein could be freed from the tumor without difficulty. In contrast, even if portography showed no portal vein invasion, resection was performed when the portal vein could not be detached from the tumor.[10] Intraoperative ultrasound was not used for decision-making in portal vein resection. Twenty wedge and 32 segmental resections were performed (Table 1). Because the transverse portion of the left portal vein is long compared with the right portal trunk, segmental resection is much easier to perform with right-sided than left-sided hepatectomy and segmental resection was more common with right-sided than left-sided hepatectomy. Two patients who underwent wedge resection required a saphenous vein patch graft to close a large defect. An external iliac vein interposition graft was used for segmental reconstruction in 3 patients. The time of portal vein clamping for portal vein resection was 23 ± 11 minutes in the 32 segmental resections. Venoveno bypass was not used in any patients.[5,13]

Histologic Evaluation

The surgical specimens were fixed in 10% formalin for several days, and serially sectioned at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examination using hematoxylin and eosin stains. Microscopic tumor invasion of the portal vein was classified as grade 0 (no involvement), grade I (cancer invasion limited to the tunica

TABLE 1. Surgical Procedures in the 52 Study Patients

Procedure	No.
Wedge resection of the portal vein (n = 20)	
Right-sided hepatectomy	6
Left-sided hepatectomy	13
Central hepatectomy	1
Direct closure	18
Patch graft	2
Segmental resection of the portal vein (n = 32)	
Right-sided hepatectomy	25
Left-sided hepatectomy	6
Central hepatectomy	1
End-to-end anastomosis	29
External iliac vein interposition graft	3
Time of portal vein clamping [mean ± SD (range)]	23 ± 11 min (13–70 min)

adventitia or media), or grade II (cancer invasion reaching the tunica intima) (Fig. 1).

In patients with grade 0 invasion, the distance between the leading edge of cancer and the outer layer of the tunica adventitia was measured. When the tunica adventitia could not be identified because it was destroyed by fibrosis, the distance was assumed the same as for the adjacent intact part of the resected portal vein. The extent of fibrosis around the resected portal vein also was evaluated.

Pathologic findings were described using the TNM Classification of Malignant Tumors by the International Union Against Cancer (6th ed, 2002).[22]

Statistics

Results are expressed as the mean ± standard deviation. Statistical analysis was performed using the Student *t* test, χ^2 test, and Fisher exact probability test, where appropriate. Postoperative survival was calculated using the Kaplan-Meier method, and differences in survival curves were compared using the log-rank test. The Cox proportional hazard model was used for multivariate analysis of survival. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathologic Features of Patients With or Without Portal Vein Resection

Clinicopathologic details of the 160 patients are summarized in Table 2, according to the presence or absence of portal vein resection. As a matter of course, tumor stage was more advanced in patients who underwent portal vein resection, compared with those who did not require portal vein resection, and liver invasion, incidence, and extent of lymph node metastasis, and grade of histologic differentiation were more advanced in the former group. All patients with portal vein resection had stage III or IV disease.

Morbidity and Mortality

Several kinds of postoperative complications occurred in 44 (84.6%) of the 52 patients; however, there were no complications directly related to portal vein resection and reconstruction. Liver failure, the most serious complication, occurred in 14 (26.9%) patients. The incidence of each complication, except for pleural effusion, was similar between the patients with and those without portal vein resection (Table 3). Four (7.7%) patients underwent a second laparotomy, due to intraabdominal bleeding (n = 3) or intraabdominal abscess (n = 1). Five (9.6%) patients died of liver failure or multiple organ failure, 16, 24, 75, 98, or 134 days after surgery. Thus, the morbidity, 30-day mortality, and

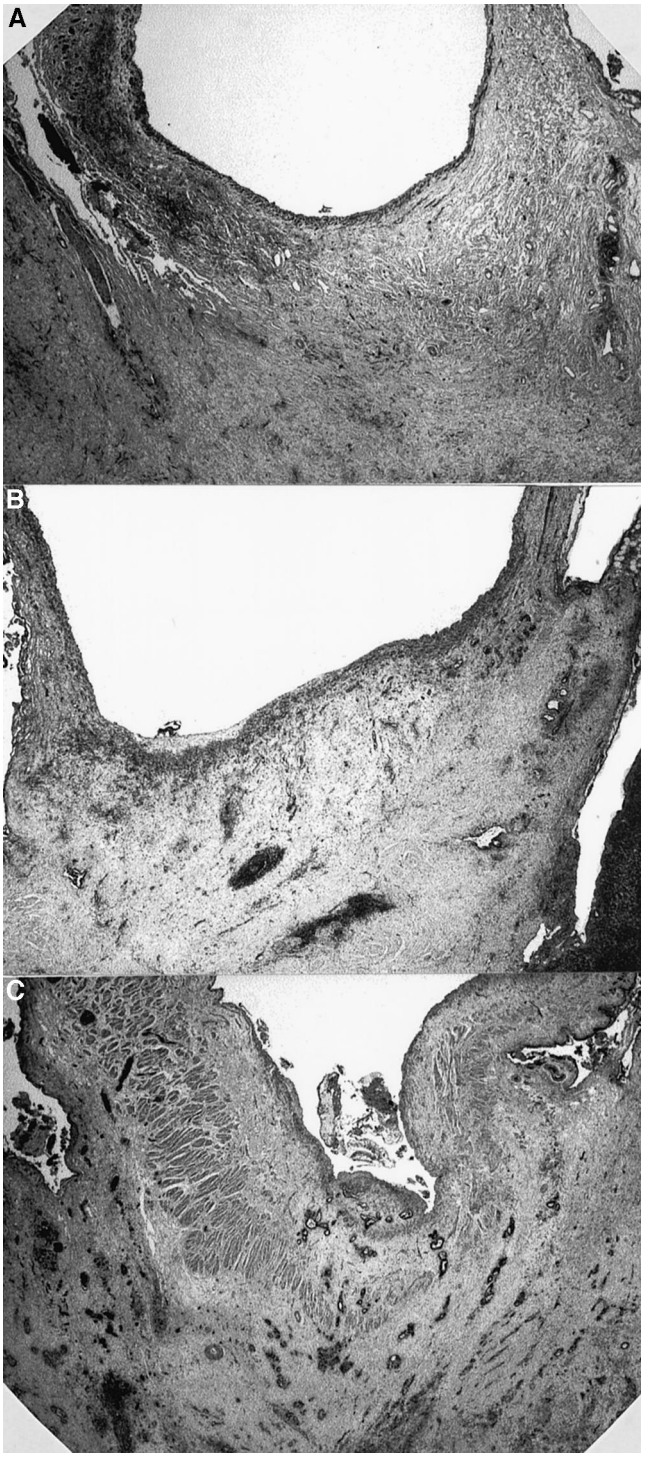

FIGURE 1. Photomicrographs of the resected portal vein (hematoxylin and eosin stains). A: Grade 0 (no involvement). B: Grade I (cancer invasion limited to the tunica adventitia or media). C: Grade II (cancer invasion reaching the tunica intima).

TABLE 2. Clinicopathologic Features of Patients Undergoing Hepatectomy With and Without Portal Vein Resection

	Portal Vein Resection		
	Present (n = 52)	**Absent (n = 108)**	***P***
Age (yr)	60.3 ± 10.6	60.2 ± 10.2	0.962
Gender (M/F)	35/17	81/27	0.307
Jaundice on admission (present)	43 (82.7%)	70 (64.8%)	0.020
Microscopic resection margin (positive)*	16 (30.8%)	13 (12.0%)	0.004
Lymphatic vessel invasion (present)	47 (90.4%)	88 (81.5%)	0.170
Microscopic venous invasion (present)	25 (48.1%)	47 (43.5%)	0.587
Perineural invasion (present)	47 (90.4%)	85 (78.7%)	0.078
Liver invasion (present)	47 (90.4%)	71 (65.7%)	0.001
Gallbladder invasion (present)	6 (11.5%)	9 (8.3%)	0.515
Histologic differentiation			
Papillary	0	14 (13.0%)	0.027
Well	7 (13.5%)	21 (19.4%)	
Moderate	43 (82.7%)	70 (64.8%)	
Poor	2 (3.8%)	3 (2.8%)	
Lymph node metastasis			
pN0	23 (44.2%)	65 (60.2%)	0.003
pN1	11 (21.2%)	30 (27.8%)	
pM1†	18 (34.6%)	13 (12.0%)	
TNM classification‡			
Stage I	0	24 (22.2%)	<0.001
Stage II	0	64 (59.3%)	
Stage III	32 (61.5%)	6 (5.6%)	
Stage IV	20 (38.5%)	14 (13.0%)	

*Including dissected margin in the transverse direction as well as resected margin of the bile duct and portal vein.
†Paraaortic node metastasis.
‡According to the TNM staging system (6th edition, 2002).

overall hospital mortality in this series were 84.6%, 3.8%, and 9.6%, respectively. These values were almost identical to those in the 108 patients who underwent macroscopically curative hepatectomy without portal vein resection (78.7%, 4.6%, and 9.3%, respectively).

Microscopic Evaluation of the Resected Portal Vein

Extent of portal vein invasion was grade 0 in 16 (30.8%) patients, grade I in 32 (61.5%), and grade II in 4 (7.7%). Therefore, approximately one third of patients with portal vein resection appeared to have portal vein involvement but did not.

Of the 16 patients with grade 0 invasion, 13 patients showed marked fibrosis adjacent to the resected portal vein, and the remaining 3 showed mild fibrosis. The distance between the leading edge of the cancer and the outer layer of the adventitia ranged from 50 to 1375 μm, with a mean of 437 ± 431 μm. The distance was <1 mm in 14 of the 16 patients with grade 0 invasion.

Survival

Survival was closely associated with portal vein resection (Fig. 2). The 3- and 5-year survival rates were 26.4% and 9.9% in patients with combined portal vein and liver resection (excluding the 5 hospital deaths), and were 53.6% and 36.8% in patients who underwent only hepatectomy (excluding 10 hospital deaths). Three patients survived more than 5 years after portal vein resection and 20 patients survived 5 years or more when the portal vein was not resected. The difference in the survival rates between the 2 groups was significant ($P < 0.0001$). The outcome of the 52 patients with unresectable tumor was dismal; no patients survived more than 3 years.

The outcome in patients with portal vein resection (excluding the 5 hospital deaths) was analyzed according to

TABLE 3. Morbidity and Mortality in Patients Undergoing Hepatectomy With and Without Portal Vein Resection

	Portal Vein Resection		
	Present (n = 52)	Absent (n = 108)	*P*
Minor complications			
Pleural effusion	38 (73.1%)	60 (55.6%)	0.033
Wound infection	16 (30.8%)	39 (36.1%)	0.505
Bile leak from liver stump	6 (11.5%)	8 (7.4%)	0.386
Major complications			
Liver failure	14 (26.9%)	21 (19.4%)	0.284
Respiratory failure	4 (7.7%)	7 (6.5%)	0.749
Renal failure	5 (9.6%)	7 (6.5%)	0.528
Bacteremia	10 (19.2%)	15 (13.9%)	0.383
Intraabdominal abscess	9 (17.3%)	15 (13.9%)	0.571
Intraabdominal bleeding	5 (9.6%)	10 (9.3%)	0.999
Insufficiency of hepaticojejunostomy	5 (9.6%)	8 (7.4%)	0.758
Insufficiency of pancreatojejunostomy	4 (44.4%)*	4 (40.0%)*	0.439
Gastrointestinal bleeding	5 (9.6%)	5 (4.6%)	0.296
Mortality	5 (9.6%)	10 (9.3%)	0.999

*Combined pancreatoduodenectomy was performed in 9 and 10 patients, respectively.

the presence or absence of microscopic portal vein invasion (Fig. 2). The survival rate for patients with microscopic invasion (grade I and II) was similar to that for patients without microscopic invasion (grade 0) (3-year survival, 22.3% vs. 35.7%; 5-year survival, 9.9% vs. 17.9%; median survival, 16.6 months vs. 19.4 months; $P = 0.1506$).

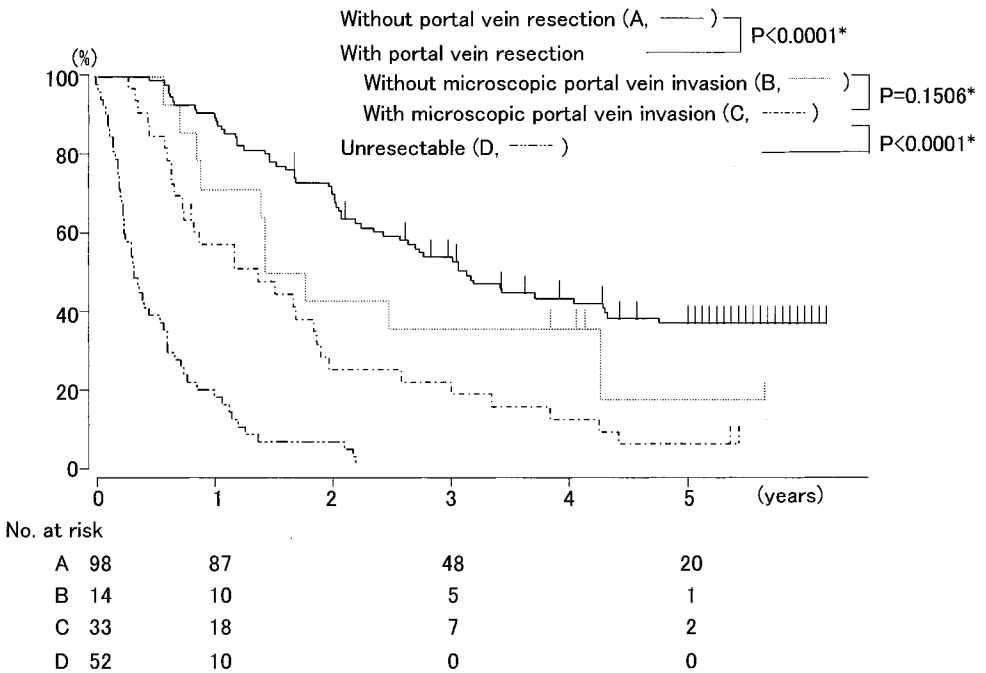

FIGURE 2. Survival in 145 patients with hilar cholangiocarcinoma who tolerated surgery and 52 patients with unresectable tumor. *By log-rank test.

Analysis of Prognostic Factors

Among the 145 patients with hilar cholangiocarcinoma who tolerated surgery, 12 independent clinicopathologic variables were analyzed as possible prognostic factors. On univariate analysis, 9 of the 12 variables proved to be significant (Table 4). Multivariate analysis using the Cox proportional hazard model was performed incorporating these 9 variables, and only histologic differentiation, lymph node metastasis, and macroscopic portal vein invasion (ie, portal vein resection) were identified as independent prognostic factors in patients with hilar cholangiocarcinoma who underwent macroscopically curative hepatectomy (Table 5).

DISCUSSION

Portal vein invasion is still a major obstacle to resection for advanced hilar cholangiocarcinoma, but portal vein resection and reconstruction are now recognized as a means to increase the resectability rate and, in turn, may offer a better chance of long-term survival. This aggressive approach is now used in leading centers in Japan,[3–5,8-10,13] Korea,[12] and Western countries.[6,7,11,14] We reviewed previous studies [excluding those from our institute][5,13] that included at least 10 patients who underwent portal vein resection for hilar cholangiocarcinoma (Table 6). Reported mortality was >10% in all studies. Despite the surgical morbidity and mortality, 5-year survival is possible. In the present study, although morbidity was quite high, there were no postoperative complications directly related to portal vein resection and reconstruction. Mortality was 9.6%, which is comparable to the rate for hepatectomy alone, and 3 patients survived more than 5 years. In addition, the outcome of patients who underwent combined portal vein and liver resection was significantly

TABLE 4. Univariate Analysis of Potential Predictors of Survival

Variable	Modality (no. of patients)	Overall Survival (%) 3-year	5-year	*P*
Age (yr)	<60 (69)	44.6	28.2	0.9883
	≥60 (76)	45.0	28.8	
Gender	Male (103)	46.2	28.7	0.5681
	Female (42)	41.5	28.5	
Microscopic resection margin*	Negative (120)	51.9	34.9	<0.0001
	Positive (25)	12.0	0	
Lymphatic vessel invasion	Absent (23)	78.0	71.5	0.0001
	Present (122)	38.6	21.1	
Microscopic venous invasion	Absent (80)	56.7	40.0	0.0009
	Present (65)	30.8	16.6	
Perineural invasion	Absent (26)	80.6	62.4	0.0002
	Present (119)	37.0	21.0	
Histologic differentiation	Papillary/well (40)	79.4	58.1	<0.0001
	Moderate/poor (105)	31.7	17.5	
Lymph node metastasis	Absent (78)	63.9	42.1	<0.0001
	Present (67)	22.0	12.4	
	pN1 (38)	30.2	13.2	
	pM1† (29)	11.0	11.0	
Liver invasion	Absent (39)	64.1	45.2	0.0036
	Present (106)	37.6	22.3	
Gallbladder invasion	Absent (132)	46.2	30.0	0.0805
	Present (13)	30.8	15.4	
Macroscopic portal vein invasion‡	Absent (98)	53.6	36.8	<0.0001
	Present (47)	26.4	9.9	
Microscopic portal vein invasion	Absent (112)	51.3	35.4	<0.0001
	Present (33)	22.3	6.4	

*Including dissected margin in the transverse direction as well as resected margin of the bile duct and portal vein.

†Paraaortic node metastasis.

‡Corresponding with portal vein resection.

TABLE 5. Multivariate Cox Regression Analysis of Prognostic Factors

Variable	Relative Risk	95% Confidence Interval	*P*
Histologic differentiation (moderate/poor)	2.57	1.44–4.61	0.0015
Lymph node metastasis (present)	1.89	1.16–3.07	0.0101
Macroscopic portal vein invasion (present)	2.18	1.09–4.35	0.0278

better than that of patients with unresectable tumor. Our results are not satisfactory but may be acceptable. We stress that portal vein involvement does not necessarily preclude resection for hilar cholangiocarcinoma and that hepatectomy with portal vein resection can be performed safely in selected patients. The increased risk associated with the procedure appears to be balanced by possible survival benefits, particularly when the lack of alternative curative approaches is considered.

The present study has revealed that occult invasion of the resected portal vein does not occur often, if at all. However, if the resected portal vein were microscopically uninvolved, the distance between the leading edge of the cancer cells and the outer layer of the adventitia was very close, <1 mm in most cases. Fibrosis in conjunction with infiltration was often present adjacent to the resected portal vein. These findings strongly suggest that without portal vein resection, the resection margin would have been positive. Therefore, even when invasion of the portal vein cannot be demonstrated preoperatively by diagnostic imaging, en bloc portal vein resection is still recommended when the portal bifurcation is involved on gross inspection during surgery.[10] Kaneko et al[23] have emphasized that intraportal endovascular ultrasonography provides accurate information regarding portal vein invasion in patients with pancreatobiliary carcinoma; however, it can be difficult to differentiate between cancer invasion and fibrosis with certainty in some cases.

Neuhaus et al[11] reported improved survival after combined liver (6 left- and 17 right-sided hepatectomies) and portal vein resection for hilar cholangiocarcinoma, in which the 5-year survival rate for R0 resections (excluding 60-day deaths) was 65% and 6 patients survived more than 5 years (Table 6). They emphasized the clinical significance of right-sided hepatectomy with portal vein resection because this procedure uses the so-called "no-touch technique" and can offer greater potential curability by resecting the portal vein. However, microscopic invasion of the resected portal vein was found in only 2 (12%) of 17 cases of right-sided hepatectomies, a finding quite different from ours. This strongly suggests that their series included many cases in which there was no macroscopic cancer invasion, probably because of the way they applied the no-touch technique. Since the left hepatic artery runs through the leftmost portion of the hepatoduodenal ligament, the portal bifurcation can be left undisturbed during right-sided hepatectomy with portal vein resection. The no-touch technique is generally used in oncologic surgery to prevent dissemination of tumor cells, so their concept may warrant further study. However, it is evident that this concept failed to improve survival in pancreas cancer. Nakao et al[24] resected the portal vein in pancreas head carcinoma, irrespective of presence or absence of portal vein invasion, but 5-year survival in patients without portal vein invasion was not improved ($<10\%$). At present we do not intend to adopt this concept.

The overall survival was worse in patients who underwent portal vein resection than in those who did not. However, the presence or absence of microscopic invasion of the resected portal vein did not affect survival. In addition, multivariate analysis demonstrated that macroscopic, but not microscopic, portal vein invasion has a negative impact on survival. Recently, UICC modified the TNM classification of malignant tumors. In the previous version (5th ed, 1997),[25] portal vein invasion was not included as a determinant of

TABLE 6. Portal Vein Resection for Hilar Cholangiocarcinoma in Previous Reports

Author	Period	Total No. of Resections (Hepotectomies)	With Portal Vein Resection		
			No.	Mortality (%)	5-year Survivors
Klempnauer[6]	1971–1995	151 (118)	39*[a]	17.1	2?
Lee[12]	1989–1997	128 (111)	29	13.8	?
Miyazaki[9]	1981–1998	93 (80)	24*[b]	16.0	1
Neuhaus[11]	1988–1998	80 (66)	23	17.4	6
Gerhards[14]	1983–1998	112 (32)	10*[c]	40.0	0
Current series	1979–2000	188 (174)	52*[d]	9.6	3

*Including portal vein plus hepatic artery resection in 1[a], 7[b], 7[c], and 1[d], respectively.

the T factor in carcinoma of the extrahepatic bile ducts. In the new version (6th ed, 2002),[22] macroscopic invasion of the main portal vein or bilateral involvement of its tributaries was categorized as a T4 lesion, and disease with T4, any N, and M0 was categorized as stage III. Our results support the newly revised TNM classification; however, since the study population is small, further research is needed to validate the results.

Considering the modest improvement in survival by portal vein resection, adjuvant therapy is of importance. However, there is no evidence that chemotherapy is effective for cholangiocarcinoma. The efficacy of adjuvant radiotherapy for cholangiocarcinoma remains controversial. Pitt et al[26] reported that postoperative radiotherapy for patients with hilar cholangiocarcinoma did not improve survival. Criticism is that most of surgeries in their series were palliative or R2 resection. However, Todoroki et al[27] described that adjuvant radiotherapy for patients with stage IV hilar cholangiocarcinoma who underwent R1 resections significantly prolonged survival compared with resection alone. Thus, adjuvant intraoperative and/or postoperative radiotherapy may have potential survival benefit when macroscopically curative resection is possible. Now we are planning adjuvant radiotherapy for locally advanced disease.

In conclusion, combined portal vein and liver resection for hilar cholangiocarcinoma can be performed with acceptable mortality. Approximately one third of the resected portal veins have not been infiltrated microscopically; however, without portal vein resection, the dissection plane will be cancer-positive in most cases. Although portal vein invasion has a negative impact on survival, combined portal vein and liver resection can offer long-term survival to some patients with advanced hilar cholangiocarcinoma who were previously thought to have inoperable disease.

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