Surgery 168 (2020) 617–624

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Bile Duct/Gallbladder

How long should follow-up be continued after R0 resection of perihilar cholangiocarcinoma?

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ARTICLE INFO

Article history:
Accepted 29 April 2020
Available online 19 July 2020

ABSTRACT

Background: Although several studies have been conducted on the patterns of recurrence in resected perihilar cholangiocarcinoma, the appropriate follow-up period after resection is still controversial.
Methods: Consecutive patients who underwent an R0 resection of perihilar cholangiocarcinoma between 2001 and 2014 were reviewed retrospectively, focusing on the time and site of initial recurrence. A Cox proportional hazards model was used for multivariate analysis.
Results: During the study period, 404 patients underwent R0 resection, of whom 242 patients (59.9%) developed a recurrence. The most common site of recurrence was locoregional, followed by peritoneum and liver. Approximately 70% of patients were asymptomatic when recurrence was detected. The median survival time in all cohorts was 4.8 years, and the estimated cumulative probability of recurrence was 54.3% at 5 years and 65.7% at 10 years. Multivariate analyses revealed that lymph node metastasis (hazard ratio 2.80, $P < .001$) and microscopic venous invasion (hazard ratio, 1.70, $P < .001$) were independent risk factors for recurrence-free survival. The cumulative probability of recurrence in 84 patients with 2 risk factors was nearly 90% at 5 years; even in the 178 patients without risk factors, the probability at 5 years was 30%, and thereafter, the probability of recurrence gradually increased, reaching nearly 50% at 10 years. No trends in the time and site of recurrence were detected.
Conclusion: Approximately 60% of patients with perihilar cholangiocarcinoma experience recurrence after R0 resection. Even in patients without an independent risk for recurrence, the recurrence probability is high, reaching nearly 50% at 10 years. Thus, close surveillance for 10 years is necessary even after R0 resection of perihilar cholangiocarcinoma.

Introduction

Perihilar cholangiocarcinoma (PHCC) is the most common type of cholangiocarcinoma and the most difficult to treat.[1,2] Because R0 resection is the only form of potential cure, hepatobiliary surgeons have aggressively adopted extended resection to achieve R0 resection. Nevertheless, the 5-year overall survival after resection is still less than 50% even in high-volume centers.[3–6] This poor survival reflects a high recurrence rate after resection. Several studies[7–13] have addressed the patterns of recurrence in patients who undergo resection of PHCC, with many limitations, including small cohorts, few major hepatectomies with caudate resection, or limited and incomplete follow-up data after resection. Previously, the present authors reported that more than half of patients with PHCC experienced recurrence even after curative-intent resection,[14] emphasizing the need for close follow-up after resection; however, the time to recurrence was not evaluated in detail. Thus, how long follow-up monitoring should be continued after resection remains unclear.

In this study, we reviewed only patients who underwent an R0 resection of PHCC and investigated the recurrence pattern, focusing on the time to recurrence, aiming to clarify the appropriate follow-up period after R0 resection.

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https://doi.org/10.1016/j.surg.2020.04.068
0039-6060/

Methods

Patients

Between January 2001 and December 2014, consecutive patients who underwent resection of PHCC in the First Department of Surgery, Nagoya University Hospital, were reviewed retrospectively with special attention to the pattern of recurrence. This study was approved by the Human Research Review Committee of Nagoya University Hospital (approval number 2019–0228).

Preoperative management

Multidetector-row computed tomography (MDCT) and cholangiography were performed in all patients. Magnetic resonance imaging and positron emission tomography were used when needed in selected patients. Patients who had jaundice routinely underwent biliary drainage either by a percutaneous approach or by an endoscopic approach.[15] Portal vein embolization was performed 2 to 3 weeks before operation in most patients undergoing extended hepatectomy ($\geq$60% resection of the liver), according to a method reported previously.[16,17] No patients received neoadjuvant chemotherapy.

Surgery

The procedures used for resection depended on the location of the primary tumor.[6] Most patients underwent right or left hemihepatectomy or right or left trisectionectomy combined with caudate lobectomy, and only a few patients underwent extrahepatic bile duct resection alone. Regional lymph nodes were dissected routinely in all patients. Dissection of periaortic lymph nodes was performed before the early 2000s, while thereafter, sampling of only 2 or 3 nodes was performed for staging. Combined pancreatoduodenectomy[18] or vascular resection[19] were performed aggressively as described previously.

Pathologic examination

Immediately after operation, the extrahepatic bile duct was opened longitudinally from the distal margin up to the proximal margin to evaluate the ductal margin status. The resected specimens were fixed in 10% formalin for several days and sectioned serially at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examination using hematoxylin and eosin staining. A positive ductal margin with invasive cancer was treated as an R1 resection, while a positive ductal margin with carcinoma in situ was treated as an R0 resection in accordance with previous studies.[20,21]

Follow-up after resection

Physical examination and blood tests, including analysis of tumor markers (carcinoembryonic antigen and carbohydrate antigen 19–9), were performed every 2 to 3 months for the first 5 years and every 6 months after 5 years. MDCT was performed every 6 months for the first 5 years and every 12 months after 5 years. When no recurrence was found at 10 years postoperatively, formal follow-up was stopped.[14]

Gemzar (gemcitabine hydrochloride, Eli Lilly and Company, Indianapolis, IN) or TS-1 (tegafur-gimeracil-oteracil potassium, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) was administered as adjuvant chemotherapy mainly in patients with lymph node metastasis after approximately 2007, because these agents were only authorized for use in 2006 to 2007. Radiation therapy was also used in some patients who had positive surgical margins.

Recurrence was diagnosed based on radiologic or cytologic examinations. Even if the tumor markers only increased above the normal limits, a diagnosis of recurrence was not made. When MDCT could not detect a recurrence definitely, we additionally performed magnetic resonance imaging for liver lesions and positron emission tomography/computed tomography for the locoregional legions. In patients who developed ascites, we aspirated ascites and performed histologic examination. Recurrence was categorized as either locoregional or distant. Locoregional recurrence was defined as a recurrence at the hepaticojejunostomy or in an area where operative procedures had been performed, including the liver hilum, hepatoduodenal ligament, common hepatic artery, and peripancreatic lesions. All other recurrences were defined as distant. In the present study, only the initial recurrence site was considered. When $\geq$2 sites were detected simultaneously as an initial recurrence, they were considered to be overlapping sites. When disease relapse was found, before 2006, 5-fluorouracil with or without mitomycin was used. After approximately 2007, Gemzar with or without cisplatin or TS-1 was used according to the treating physician's preference.

Statistics

Continuous data are expressed as the median with the range unless otherwise specified. Statistical analyses were performed using a Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Recurrence-free survival (RFS) was measured from the time of operation to the time of first recurrence or death from any cause. No patients who died were censored, regardless of the cause, in assessing overall survival (OS). The cumulative recurrence rate, RFS, and OS were estimated using the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. A Cox proportional hazards model was used for multivariate analysis. In this model, stepwise forward selection was used with entry and removal limits of $P < .050$ and $P > .100$, respectively. All of the reported *P* values were two-sided. All statistical calculations were performed using SPSS version 25 (IBM Japan, Tokyo, Japan).

Results

During the study period, 587 consecutive patients with PHCC underwent resection. Of these, 183 patients were excluded, including 77 patients with pM1 disease, 85 patients with R1 resection, 8 patients with R2 resection, 12 (2.0%) patients who died of postoperative complications, and 1 patient without detailed follow-up information. The remaining 404 patients who underwent an R0 resection, including 254 men and 150 women with a median age of 68 years (range, 34–85 years), were enrolled in the present study.

Of the 404 study patients, 397 (98.3%) underwent hepatectomy with en bloc resection of the caudate lobe and extrahepatic bile duct, and the remaining 7 patients underwent extrahepatic bile duct resection alone. Combined pancreatoduodenectomy was performed in 51 patients, and combined portal vein or hepatic artery resection was performed in 146 patients.

Clinicopathologic features according to recurrence type

During the follow-up period, 162 (40.1%) patients had no recurrence (group A), and the remaining 242 patients had recurrence, including 212 (52.5%) patients in whom recurrence developed within 5 years (group B) and 30 (7.4%) patients in whom recurrence developed after 5 years (group C). The clinicopathologic features according to the time of recurrence are shown in Table I.

Table I
Clinicopathologic characteristics according to recurrence type

Variables	Recurrence type			P value	
	Group A: No recurrence ($n = 162$)	Group B: Recurrence within 5 y ($n = 212$)	Group C: Recurrence after 5 y ($n = 30$)	(A vs B+C)	(B vs C)
Age, y (range)	68 (34–84)	67 (37–85)	69 (48–83)	.902	.813
Sex, male *n* (%)	97 (59.8)	141 (66.5)	16 (53)	.308	.157
Bismuth classification, *n* (%)				.044	.095
I/II	40 (24.7)	32 (15.1)	8 (7)		
III/IV	122 (75.3)	180 (84.9)	22 (73)		
Preoperative biliary drainage, *n* (%)				.302	<.001
None	21 (13.0)	21 (9.9)	11 (37)		
Percutaneous transhepatic	60 (37.0)	95 (44.8)	12 (40)		
Endoscopic	81 (50.0)	96 (45.3)	7 (23)		
Preoperative albumin, g/dL (range)	3.6 (2.4–4.7)	3.6 (2.4–4.4)	3.6 (2.5–4.3)	.121	.994
Preoperative CRP,* mg/dL (range)	0.2 (0.0–8.9)	0.3 (0.0–13.6)	0.2 (0.0–5.1)	.017	.625
Modified GPS,* *n* (%)				.132	.879
0	140 (86.4)	166 (79.0)	23 (77)		
1	10 (6.2)	17 (8.1)	3 (10)		
2	12 (7.4)	27 (12.9)	4 (13)		
Type of hepatectomy, *n* (%)				.217	.565
S1,4,5,6,7,8	6 (3.7)	14 (6.6)	4 (13)		
S1,5,6,7,8	68 (42.0)	66 (31.1)	9 (30)		
S1,2,3,4,5,8	38 (23.5)	59 (27.8)	6 (20)		
S1,2,3,4	46 (28.4)	64 (30.2)	9 (30)		
S1,4,5,8 / S1,5,8 / S1	2 (1.2)	5 (2.4)	1 (3)		
Without hepatectomy	2 (1.2)	4 (1.9)	1 (3)		
Combined resection, *n* (%)					
Pancreatoduodenectomy	22 (13.6)	24 (11.3)	5 (17)	.636	.280
PV or HA resection	46 (28.4)	92 (43.4)	8 (27)	.008	.082
Operative time, min (range)	554 (353–1,015)	600 (348–1,005)	538 (373–963)	.069	.054
Blood loss, mL (range)	1,183 (258–11,115)	1,365 (46–7,100)	1,357 (451–4,304)	.015	.736
Perioperative blood transfusion, *n* (%)	49 (30.2)	73 (34.4)	6 (20)	.612	.115
Histology, *n* (%)				.001	.054
Papillary/well	66 (40.7)	50 (23.6)	12 (40)		
Moderately/poorly	96 (59.3)	162 (76.4)	18 (60)		
Microscopic lymphatic invasion, *n* (%)	87 (53.7)	165 (77.8)	16 (53)	<.001	.004
Microscopic venous invasion, *n* (%)	38 (23.5)	107 (50.5)	6 (20)	<.001	.002
Microscopic perineural invasion, *n* (%)	121 (74.7)	193 (91.0)	23 (77)	<.001	.027
Lymph node metastasis, *n* (%)	29 (17.9)	122 (57.5)	8 (27)	<.001	.001
Adjuvant chemotherapy, *n* (%)	25 (15.4)	66 (31.1)	6 (20)	.001	.212
Reresection, *n* (%)	-	16 (7.5)	4 (13)	-	.224

CRP, C-reactive protein; *GPS*, Glasgow Prognostic Score; *HA*, hepatic artery; *PV*, portal vein.
* Two patients were excluded owing to data missing.

Bismuth classification, combined vascular resection, blood loss, presence of microscopic lymphatic, venous, or perineural invasions, and lymph node metastasis were statistically significantly different between patients without recurrence (group A) and those with recurrence (groups B and C). Although the preoperative C-reactive protein level was also "statistically" significantly different, the difference was small, being clinically unimportant. Comparing group B with group C, preoperative biliary drainage, the presence of microscopic lymphatic, venous, or perineural invasions, and lymph node metastasis were statistically significantly different.

Initial recurrence site and symptom

The initial recurrence sites according to the time of initial recurrence are summarized in Table II. The rate of isolated locoregional recurrence was less in group B patients than in group C patients (26.9% vs 43.3%; $P = .063$). In contrast, the rate of distant metastasis was similar between the 2 groups (68.4% vs 56.7%; $P = .869$). Peritoneum and liver were the most common distant recurrent sites in both groups.

The presence or absence of symptoms at the time of initial recurrence was investigated in 224 of the 242 patients with recurrence (18 patients were excluded owing to insufficient information). Of the 224 patients, 157 (70.0%) patients were asymptomatic at the time of recurrence, all of whom were diagnosed with recurrence based on routine follow-up MDCT or increased tumor markers. The proportion of asymptomatic patients was similar between groups B and C (69.9% vs 71.4%; $P = .869$). More than 30% of patients with locoregional or peritoneal recurrence had symptoms, although few patients with liver, lung, or retroperitoneal lymph node recurrence were symptomatic.

Resection of initial recurrence

Of the 242 patients with recurrence, 20 (8.3%) patients underwent resection of the initial recurrence. The details of the 20 patients are shown in Table III. Their median RFS time after initial operation was 2.2 years (range, 0.3 to 7.2 years). Resected recurrence sites included liver ($n = 6$), lung ($n = 6$), peritoneum ($n = 4$), abdominal wall ($n = 3$), and adrenal gland ($n = 1$). Six patients had no recurrence after resection of the recurrence, and the remaining 14 patients had another recurrence. In the 20 patients, the median survival time after initial resection was 5.4 years (0.8 to 15.7 years), and the median survival time after resection of recurrence was 3.2 years (0.4 to 9.4 years).

Survival

The median follow-up time of all study patients and survivors was 4.6 years (interquartile range, 1.8–7.9 years) and 8.5 years

Table II
Initial recurrence site according to recurrence type

Site	Time of recurrence	
	Within 5 y (group B, $n = 212$)	After 5 y (group C, $n = 30$)
Locoregional, *n* (%)	67 (31.6)	13 (43)
Isolated, *n* (%)	57 (26.9)	13 (43)
With distant metastasis, *n* (%)	10 (4.7)	0
Distant, *n* (%)	145 (68.4)	17 (57)
Peritoneum, *n* (%)	59 (27.8)	6 (20)
Liver, *n* (%)	50 (23.6)	8 (27)
Lung or mediastinum, *n* (%)	21 (9.9)	4 (13)
Retroperitoneal lymph node, *n* (%)	24 (11.3)	1 (3)
Abdominal wall, *n* (%)	9 (4.2)	0
Bone, *n* (%)	7 (3.3)	1 (3)
Pleura, *n* (%)	1 (0.5)	0
Spleen, *n* (%)	0	1 (3)
Adrenal gland, *n* (%)	2 (0.9)	0

(interquartile range, 6.2–12.4 years), respectively. Of the 404 study patients, 271 (67.1%) died. The median survival time was 4.8 years, and the OS was 62.4% at 3 years, 48.9% at 5 years, and 31.2% at 10 years (Fig 1, *A*). The estimated cumulative probability of recurrence was 46.6% at 3 years, 54.3% at 5 years, and 65.7% at 10 years (Fig 1, *B*). Of the 242 patients with recurrence, 184 (76.0%) patients had a recurrence within 3 years, 28 (11.6%) patients had a recurrence in 4 to 5 years, and 30 (12.4%) patients had a recurrence after 5 years. Notably, 2 patients had a recurrence at 10.1 years and 11.3 years after operation.

The OS after initial resection statistically significantly worsened with earlier recurrence; the median survival time was 2.1 years in the 184 patients with recurrence within 3 years, 5.6 years in the 28 patients with recurrence in 4 to 5 years, and 9.2 years in the 30 patients with recurrence after 5 years (Fig 2, *A*). The OS after recurrence was statistically significantly worse in the 184 patients with recurrence within 3 years, and it was similar in the 28 patients with recurrence in 4 to 5 years and in the 30 patients with recurrence after 5 years (Fig 2, *B*).

Prognostic factors for RFS

Univariate and multivariate analyses revealed that lymph node metastasis (hazard ratio 2.80; $P < .001$) and microscopic venous invasion (hazard ratio, 1.70; $P < .001$) were independent risk factors for RFS in patients with R0 resection (Supplementary Table I).

Cumulative probability of recurrence according to risk factors

The estimated cumulative probability of recurrence was analyzed according to the combination of the abovementioned two risk factors for RFS. The probability was the greatest in 84 patients with two risk factors, followed by 142 patients with one risk factor, and 178 patients without a risk factor (Fig 3). In the 84 patients with 2 risk factors, the probability was very high, nearly 90% at 5 years. Even in the 178 patients without risk factors, the probability at 5 years was approximately 30%; thereafter, it gradually increased, reaching nearly 50% at 10 years.

Analyses of recurrence patterns in patients without risk factors

Of the 178 patients without risk factors, 69 (38.8%) patients had a recurrence, including 51 patients with recurrence within 5 years and 18 patients with recurrence after 5 years. The time and site of recurrence in these 69 patients are summarized in Fig 4. Unfortunately, no trends were detected in the time and site of recurrence, which may be useful for follow-up.

Discussion

The present study demonstrated that (1) approximately 60% of patients with PHCC experience recurrence even after an R0 resection, (2) most of patients were asymptomatic when recurrence was detected, (3) OS after initial resection decreased with earlier recurrence, (4) lymph node metastasis and microscopic venous invasion were independent risk factors for RFS, (5) the cumulative probability of recurrence was high, gradually increasing after 5 years even in patients without risk factors, and (6) no trends in the time and site of recurrence, which may be useful for follow-up, were detected. Overall, this study has again realized the “intractable” and “insistent” nature of PHCC, which implies the importance of close- and long-term follow-up after R0 resection with the chance for re-resection in selected patients.

Why did more than half of patients with R0 resection experience recurrence? One possible reason is inaccurate histologic evaluation of the surgical margins, including the ductal margin and radial margin. Many authors have investigated the status of the ductal margin in resected extrahepatic cholangiocarcinomas,[22–24] and the ductal margin is evaluated routinely in daily clinical practice at most centers. In contrast, evaluation of the radial margin may be somewhat remiss; for example, a French, multi-institutional survey on pathologic reports of PHCC demonstrated that only 10% of pathology reports described the status of the radial margin status.[25] In our clinic, all resected specimens were serially sectioned at 5-mm intervals, and the ductal and radial margins were identified by surgeons who understand the 3-dimensional liver anatomy and surgical procedures, and then the specimens were submitted to the pathology department.[26] Despite such meticulous handling of the resected specimens, evaluation of surgical margins is difficult and likely to underestimate the true situation. Although all operations evaluated in the present study were R0 resections, we realize that some resections must not have been “true” R0 resections.

Variables associated with tumor aggressiveness, such as lymph node metastasis or microscopic lymphatic, venous, or perineural invasions, were observed more frequently in patients with early recurrence than in patients with later recurrence. Reflecting this biologic aggressiveness, the OS after the initial R0 resection worsened as recurrence became earlier. In particular, survival in the patients with recurrence within 3 years was dismal. Thus, the use of effective adjuvant chemotherapy is mandatory. In this cohort, however, only 31% of patients with recurrence within 5 years received adjuvant chemotherapy. The previous randomized controlled trial failed to support any clinical value of gemcitabine as an adjuvant for resected extrahepatic cholangiocarcinoma[27]; thus,

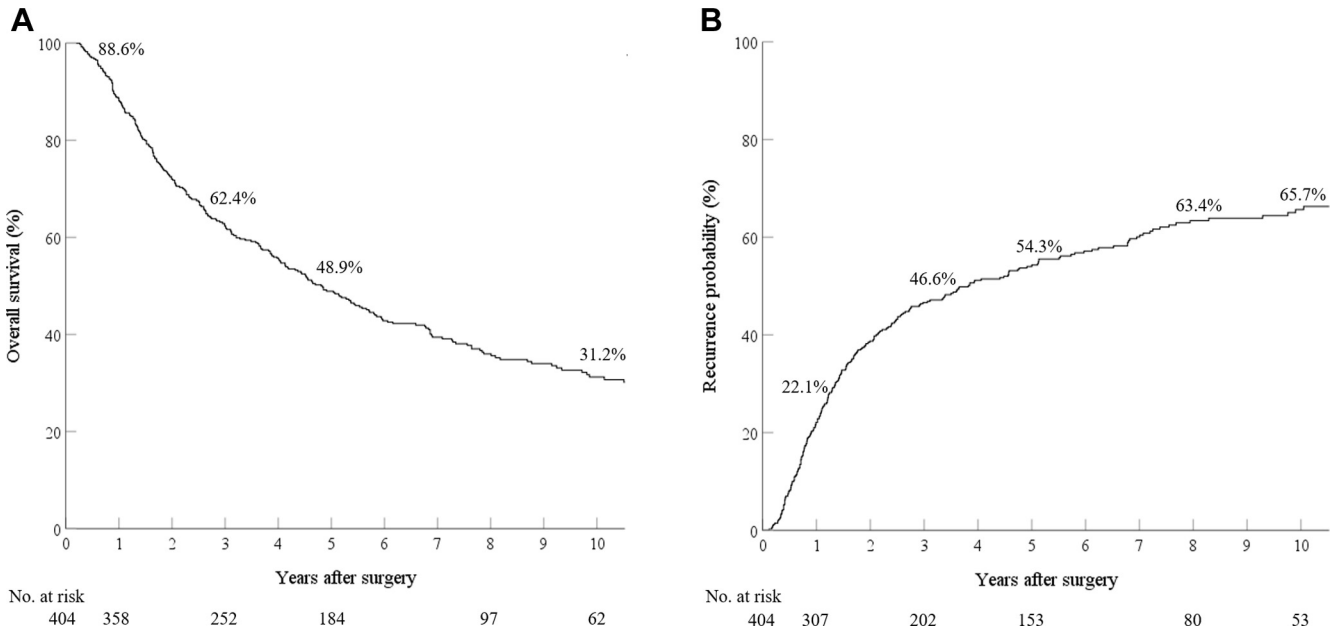

Fig 1. OS (*A*) and estimated cumulative probability of recurrence (*B*).

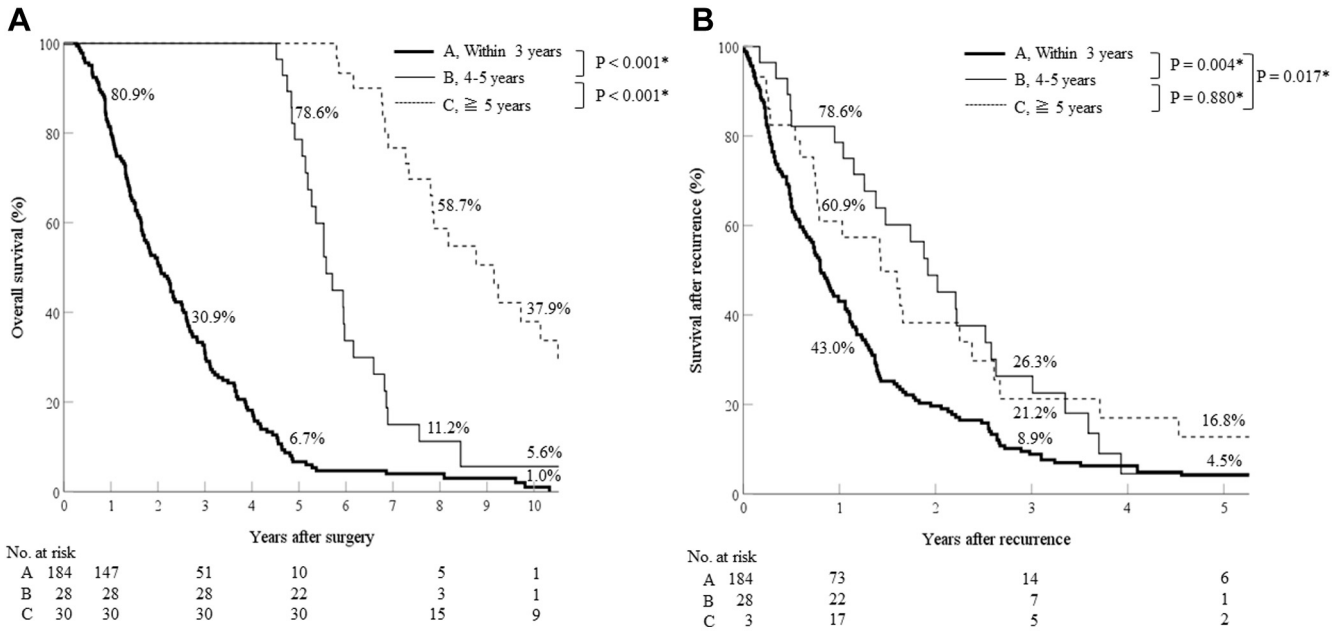

Fig 2. OS after initial resection (*A*) and after recurrence (*B*) according to time of recurrence. *The log-rank test.

the present authors now use TS-1, especially in patients with lymph node metastasis.

More than two-thirds of patients with recurrence were asymptomatic at the time of recurrence and were diagnosed based on routine follow-up MDCT or increased tumor markers. The proportions of asymptomatic patients were similar between patients with early recurrence and those with late recurrence. These findings may indicate that follow-up MDCT at prespecified intervals (usually 6 months) is important, although a Western report described that imaging studies should be performed only with suspicion of recurrence.[13] Importantly, almost all patients with liver or lung recurrence were asymptomatic, but owing to follow-up computed tomography, recurrence was detected at the resectable stage, leading to resection and long-term survival in a few patients with such recurrences (Table III). It is still unclear whether early detection and treatment of recurrence improves outcome. However, considering that chemotherapy is much less effective than resection, resection of recurrence after early detection appears promising.[28]

The present multivariate analysis demonstrated that lymph node metastasis and microscopic venous invasion were independent risk factors for RFS as was confirmed in a previous report.[14] The combination of these 2 risk factors could well stratify the cumulative probability of recurrence. The probability of recurrence in

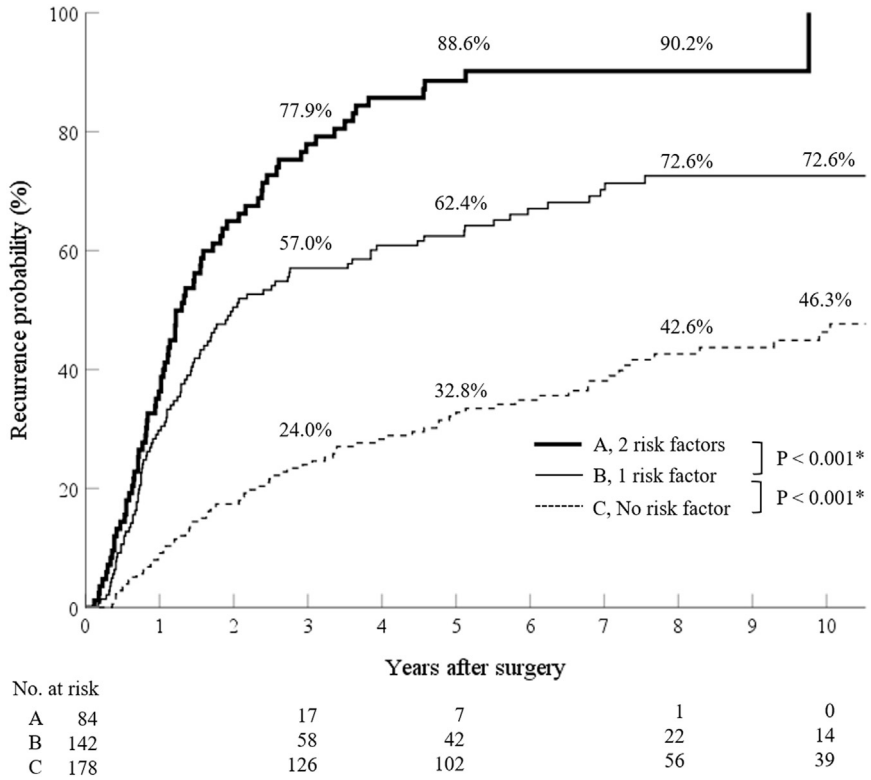

Fig 3. Estimated cumulative probability of recurrence according to the number of independent risk factors, including lymph node metastasis and microscopic venous invasion. *The log-rank test.

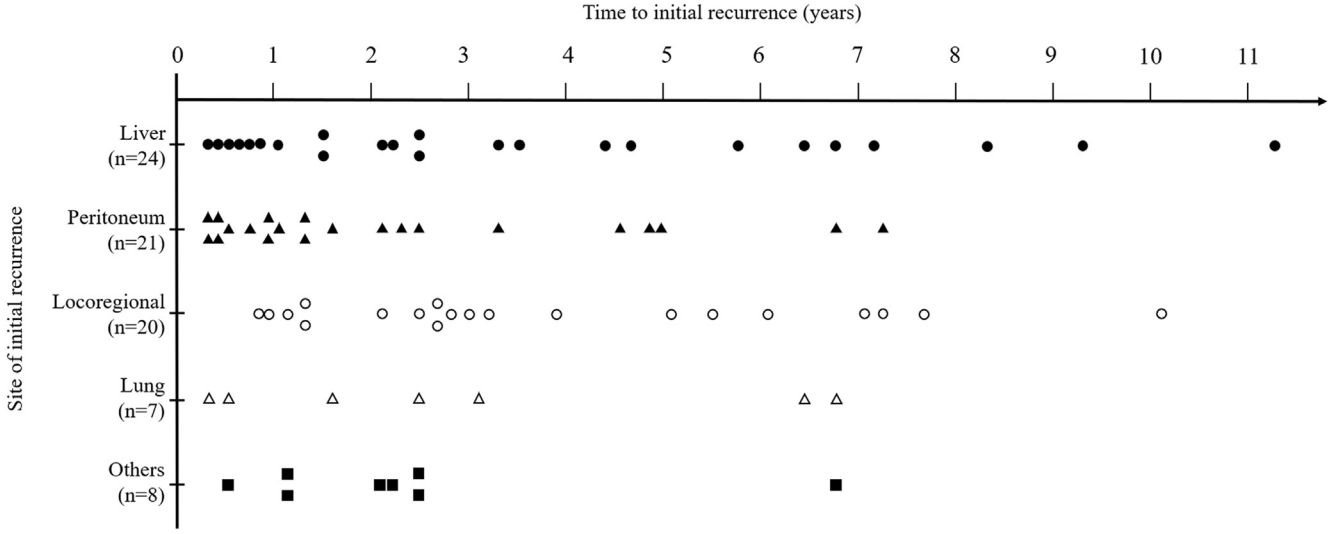

Fig 4. Site and time of initial recurrence in patients without risk factors.

patients with the 2 risk factors was nearly 90% at 5 years. Unexpectedly, the probability of recurrence even in patients without risk factors was high, 32.8% at 5 years and 46.3% at 10 years. Attention should be paid to the gradual increase in the probability of recurrence even after 5 years. In addition, no trends in the time and site of recurrence were detected. These observations indicate that 10-year surveillance is necessary even in patients who undergo R0 resection and do not have any risk factors. A declaration of cure for resected PHCC should not be made until least 10 years after the initial R0 resection. Pancreatic ductal adenocarcinoma is characterized by rapid growth with an uncontrollable nature, and Groot et al reported that 97% of all observed recurrences occurred within 5 years after resection.[29] In contrast, Lee et al showed that the recurrence rate in resected hepatocellular carcinoma increased gradually until 10 years after hepatectomy,[30] similar to the recurrence pattern of PHCC.

The main limitation of the present study is its single-center and retrospective nature, which prevents unexpected bias from being ruled out. Compensating for this shortfall is the fact that the present cohort is the largest homogeneous cohort reported to date

Table III
Details of 20 patients who underwent resection for recurrence

Patient No.	Age	Sex	Surgery for primary cancer*	Recurrence-free survival (y)	Initial recurrence	Surgery for recurrence	Survival after recurrence (y)	Recurrence	Overall survival† (y)	Prognosis
1	50	F	S1,2,3,4,5,8 + PV	0.3	Abdominal wall	Abdominal wall resection	0.5	Bone	0.8	Death
2	61	M	S1,2,3,4,5,8	0.5	Abdominal wall	Abdominal wall resection	0.8	Lung, abdominal wall	1.3	Death
3	63	F	S1,2,3,4 + HA	0.5	Peritoneum	Metastasectomy	0.5	Liver	1.0	Death
4	75	M	S1,2,3,4 + PV	0.9	Right adrenal	Right adrenalectomy	9.4	-	10.3	Alive
5	70	M	S1,2,3,4 + HA	1.3	Lung	Partial lung resection	1.3	Pleura	2.6	Death
6	53	F	S1,2,3,4	1.3	Liver	Partial hepatectomy	1.3	Lung	2.6	Death
7	57	F	S1,2,3,4,5,8 + PV	1.4	Peritoneum	Metastasectomy	3.2	Peritoneum	4.6	Death
8	43	M	S1,2,3,4,5,8	1.6	Lung	Partial lung resection	3.1	Lung	4.7	Death
9	69	F	S1,5,6,7,8 + PV	1.9	Abdominal wall	Abdominal wall resection	1.1	Abdominal wall	3.0	Death
10	73	M	S1,5,6,7,8 + PV	2.0	Lung	Partial lung resection	2.1	-	4.1	Death
11	41	M	S1,2,3,4,5,8 + PV + HA	2.5	Liver	Partial hepatectomy	7.1	-	9.6	Alive
12	68	F	S1,5,6,7,8 + PD	2.9	Liver	Partial hepatectomy	5.1	Locoregional	8.0	Alive
13	72	M	S1,4,5,6,7,8	3.2	Lung	Partial lung resection	4.1	Lung	7.3	Death
14	65	M	Bile duct resection	3.6	Liver	Partial hepatectomy	4.0	Locoregional	7.6	Death
15	43	F	S1,5,6,7,8	4.4	Liver	Partial hepatectomy	1.0	Locoregional	5.4	Death
16	60	F	S1,2,3,4	4.9	Peritoneum	Metastasectomy	3.3	-	8.2	Alive
17	55	M	S1,2,3,4	5.0	Peritoneum	Left nephron-ureterectomy	7.8	Liver	12.8	Death
18	74	M	S1,2,3,4	6.8	Lung	Partial lung resection	8.9	-	15.7	Alive
19	71	M	S1,2,3,4,5,8 + HA	7.0	Lung	Partial lung resection	5.0	-	12.0	Alive
20	58	M	S1,2,3,4	7.2	Liver	Partial hepatectomy	4.5	Liver	11.7	Death

HA, hepatic artery resection; *PD*, pancreatoduodenectomy; *PV*, portal vein resection.
* Expressed as Couinaud's hepatic segments resected.
† Overall survival equals recurrence-free survival and survival after recurrence.

including only R0 patients. In addition, follow-up surveillance in this cohort was long and careful, more than 10 years for survivors, and close monitoring was accomplished with routine follow-up MDCT. Another criticism is the unstandardized use of adjuvant chemotherapy. During the study period, however, there were no convincing data on an adjuvant chemotherapy scheme for cholangiocarcinoma.

In conclusion, approximately 60% of patients with PHCC experience recurrence after an R0 resection. Even in patients without independent risks for recurrence, the probability of recurrence is high, reaching nearly 50% at 10 years. Thus, close surveillance for 10 years is necessary even after R0 resection of PHCC.

Conflict of interest/Disclosure

We have no conflict of interest to disclosure.

Funding/Support

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2020.04.068.

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