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Occult synchronous liver metastasis from perihilar cholangiocarcinoma

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ABSTRACT

Background: No authors have reported occult liver metastases from perihilar cholangiocarcinoma (PHCC), which are defined as intrahepatic metastases that are overlooked by preoperative workup and intraoperative inspection but are detected by final pathology. The aim of this study was to clarify the features of such unappreciated metastases.

Methods: We reviewed retrospectively the medical records of patients with PHCC treated between 2001 and 2016 with attention to liver metastases.

Results: During the study interval, 945 consecutive patients with PHCC were treated, including 260 unresected and 685 resected patients (672 with hepatectomy and 13 without). Of these, 36 patients had overt liver metastases. Of the 672 hepatectomized patients, 21 (3.1%) patients had occult liver metastases with a median number of 1 (range 1–6). When compared between occult and overt metastases, the diameter was smaller in the former (5 mm vs 12 mm, $P < .001$). When compared between the 21 patients with occult metastases and the 645 hepatectomized patients without liver metastases, microscopic venous invasion and lymph node metastases were observed frequently in the patients with occult metastases. Survival for these 21 patients with occult metastases was better than that for the 36 patients with overt metastases (median survival time; 17.1 vs 7.4 months, $P < .01$).

Conclusion: Occult liver metastases from PHCC are not extremely rare. Meticulous handling of the resected specimens is crucial to detect such metastases. Although patients with occult metastases had advanced stages of the disease, their survival was better than that for patients with overt metastases.

Introduction

Perihilar cholangiocarcinoma (PHCC) is a devastating disease and still considered to be one of the most difficult cancers to treat.[1–5] Although technically demanding, curative resection is the only option with a chance of long-term survival. Therefore, in the past several decades, many surgeons have aggressively pursued these technically difficult resections and have reported outcomes with varying degrees of success.[1–5]

Although selected synchronous liver metastases from colorectal cancer are ideal candidates for resection, those from PHCC, in contrast, are deemed unresectable, which is a well-accepted consensus. From our experience, however, we have noticed that small liver metastases are on occasion overlooked during laparotomy and are found only by final pathology in the resected specimen in several patients who have undergone hepatectomy. To date, no authors have reported such occult synchronous liver metastases from PHCC; thus, nothing is known about these special unappreciated metastases.

The aim of the present retrospective study was to review the medical records of patients with PHCC with a focus on liver metastases and to clarify the incidence and features of occult synchronous liver metastases from PHCC.

Patients and Methods

Study patients

Between 2001 and 2016, we reviewed retrospectively all consecutive patients with PHCC who were treated at the First Department of Surgery, Nagoya University Hospital with a special

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attention to liver metastases. This study was approved by the Human Research Review Committee of Nagoya University Hospital (approval no. 2018-0075).

All patients were divided into the following 5 groups according to the status of liver metastasis: group A were inoperable patients owing to liver metastases detected by preoperative workup; group B were those who underwent laparotomy but were found by intraoperative inspection to be unresecteable owing to liver metastases; group C were hepatectomized patients with liver metastases detected by preoperative workup or intraoperative inspection; group D were hepatectomized patients with liver metastases found by final pathology of the resected specimens; and group E were hepatectomized patients without liver metastases by final pathology. Groups A, B, and C were defined as patients with overt liver metastases, and group D was defined as patients with occult liver metastases.

Workup for tumor staging and preoperative management

For tumor staging, ultrasonography, computed tomography (CT), and cholangiography were performed routinely. Other imaging approaches, including magnetic resonance imaging (MRI) and positron emission tomography scan, were utilized in certain selected patients when needed.

Patients who had jaundice or dilated bile ducts in the future remnant lobe routinely underwent biliary drainage by percutaneous or endoscopic approach. Portal vein embolization was performed when the liver remnant was <40%.[5]

Operation

When periaortic lymph node metastases, liver metastases, or peritoneal dissemination were observed during laparotomy, resection was abandoned in principle; however, even in the presence of distant metastasis, resection was undertaken in highly selected patients provided that resection was not deemed to be too risky and was considered likely to improve the patient's quality of life. Intraoperative ultrasonography was not used to look for liver metastases.

All hepatectomies were performed after the serum total bilirubin concentrations were <2 mg/dL. The liver parenchyma was transected with an ultrasonic dissector (CUSA, Valleylab, Boulder, CO) via the Pringle maneuver for 15 or 20 min at 5-minute intervals. Combined vascular resection or combined pancreatoduodenectomy was performed when needed.[5] Bilioenteric continuity was reestablished using a Roux-en-Y cholangiojejunostomy.

Chemotherapy

Gemcitabine hydrochloride and tegafur-gimeracil-oteracil potassium (S-1) were authorized for use in treating cholangiocarcinoma in Japan in 2007. Thereafter, we have used these agents as adjuvant chemotherapy and chemotherapy for unresected patients. Postoperative adjuvant chemotherapy was performed in patients with nodal metastasis, a positive resection margin, or occult liver metastasis, where gemcitabine hydrochloride or S-1 was given for at least 6 months postoperatively. Postoperative radiotherapy combined with chemotherapy was used in selected patients with a positive resection margin.

Pathologic assessment

The extrahepatic bile duct of the resected specimen was opened longitudinally beginning from the distal resection margin and moving up to the proximal margin to accurately evaluate the ductal margin status. Then, the resected specimens were fixed in 10% formalin for several days and serially sectioned at 5-mm intervals (Fig 1). Intrahepatic biliovascular structures were identified on the serial sections and documented on real-size color photocopies of the sections.[6] The cut surfaces of the specimen were inspected carefully, and when a nodule was suspected to be a liver metastasis, that specimen was sectioned for a microscopic examination (Fig 2, *A*). The specimens were prepared in the usual manner by hematoxylin and eosin staining. Histologic findings were described using the tumor-node-metastasis classification of malignant tumors by the International Union Against Cancer (seventh edition, 2009).[7]

Fig 1. Handling of the resected specimen. The resected specimen was serially sectioned at 5-mm intervals, and the cut surface was inspected carefully.

Statistical analysis

Results are expressed as median with ranges unless otherwise specified. The statistical analysis was performed by Mann-Whitney *U* test for continuous variables and by Fisher exact probability test for categorical variables. Patient survival was calculated by the Kaplan-Meier method. Differences in survival curves were compared using the log-rank test. A multivariate analysis was performed using Cox proportional hazards model to identify prognostic factors. All statistical calculations were performed using the SPSS version 22 software (IBM Japan, Tokyo).

Results

During the study period, 945 consecutive patients with PHCC were treated at the First Department of Surgery, Nagoya University Hospital: 260 patients had unresectable disease, and the remaining 685 patients underwent resection. Of the 685 resected patients, 13 underwent extrahepatic bile duct resection without hepatectomy. The remaining 672 patients underwent hepatectomy, including right trisectionectomy ($n = 57$), right hemihepatectomy ($n = 213$), left trisectionectomy ($n = 177$), left hemihepatectomy ($n = 208$), central bisectionectomy ($n = 11$), and other hepatectomies ($n = 6$), with ($n = 85$) or without pancreatoduodenectomy ($n = 587$). Vascular resection was performed aggressively for locally advanced PHCC including portal vein resection alone ($n = 145$), hepatic artery resection alone ($n = 40$), and simultaneous resection of the portal vein and hepatic artery ($n = 93$).[8]

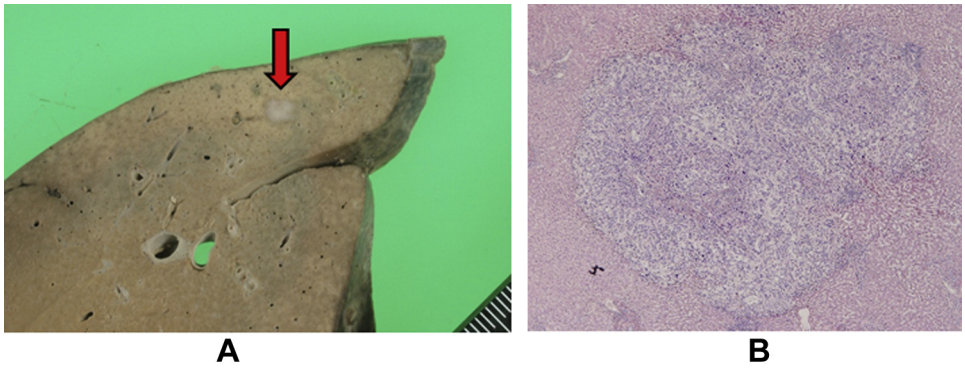

Fig 2. Representative case of occult synchronous liver metastasis. (*A*) Cut surface of the resected specimen. A small intrahepatic nodule (red arrow) was observed. (*B*) Microscopic findings of the liver nodule (Hematoxylin-eosin stain).

Incidence of synchronous liver metastasis

Liver metastases were found in 30 (11.5%) of the 260 unresected patients and were the fifth common cause of unresectability. Of these, 15 patients were categorized as group A, and the remaining 15 patients were as group B (Fig 3). Of the 672 hepatectomized patients, 6 (0.9%) were categorized as group C, another 21 as group D, and the remaining 645 as group E (Fig 3).

Therefore, the incidence of occult synchronous liver metastases was 3.1% (21 out of 672) in hepatectomized patients. Overall, synchronous liver metastases, including both overt and occult metastases, were observed in 57 (6.0%) of the entire group of 945 patients treated.

Clinical features of liver metastasis

Clinical features of liver metastases in each group are summarized in Table I. In group A ($n = 15$), all liver metastases were detected with a median number of 4 by preoperative CT, thus leading to unresectability. In group B ($n = 15$), liver masses in 10 patients were not detected by preoperative CT, whereas in the remaining 5 patients, liver masses were detected, but the preoperative CT diagnosis was liver abscess in 4 patients and parenchymal ischemia in one patient. During laparotomy, liver metastases were detected and confirmed by frozen section, and resections were abandoned. In group C ($n = 6$), preoperative diagnoses of liver metastasis had been made in 5 patients; in the remaining 1 patient, an overt metastasis was found during laparotomy. Nevertheless, resections were performed under an aggressive strategy at that time. In group D ($n = 21$), no liver masses were detected by preoperative CT, and no liver metastases were found at the time of laparotomy; however, final pathology of the resected specimens demonstrated liver metastases with a median number of 1 (range 1–6; Fig 2, *B*). All occult liver metastases were located within the liver parenchyma and were not seen on the

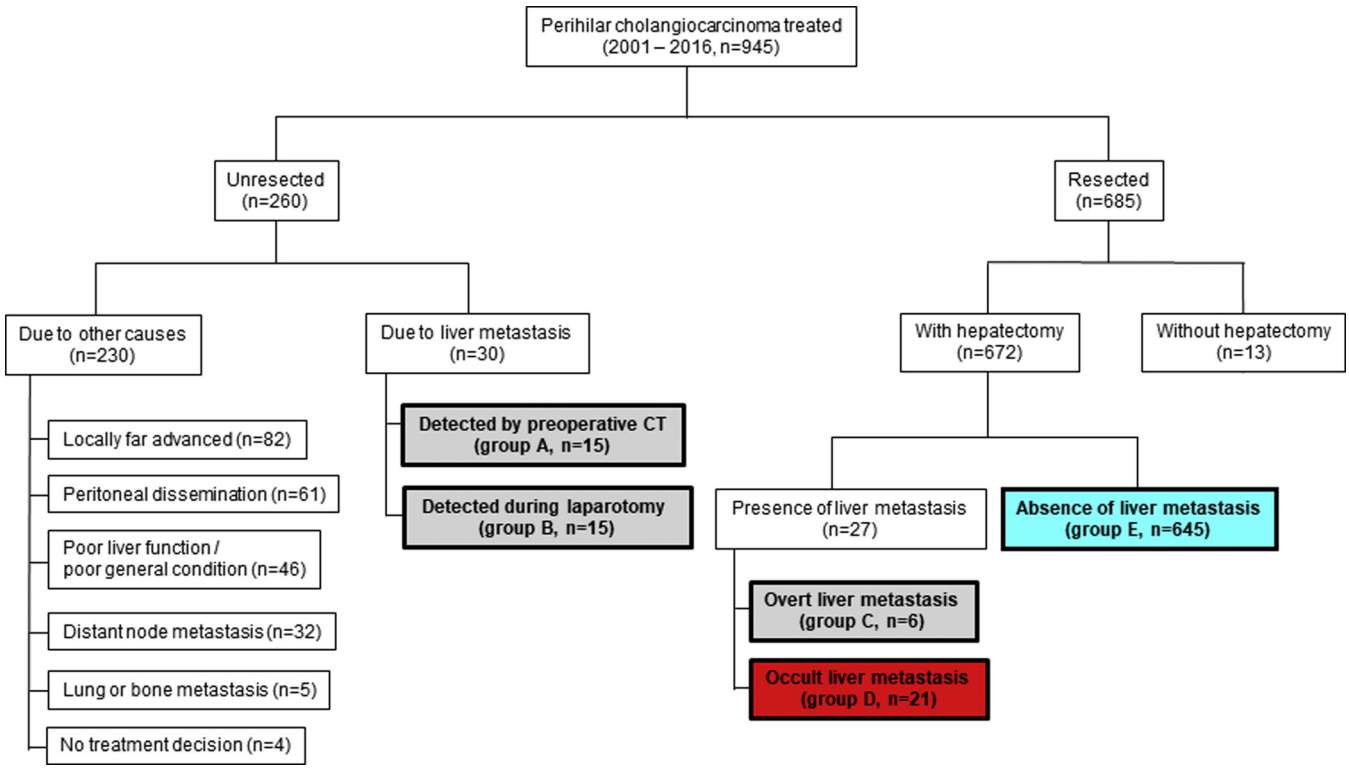

Fig 3. Overview of the patients treated during the study period according to resectability and liver metastases.

Table I
Comparison between patients with overt liver metastasis and those with occult liver metastasis

Variables	Overt metastasis			Occult metastasis	*P* value*
	Group A	Group B	Group C	Group D	
No. of patients, *n*	15	15	6	21	—
Age, y (range)	63 (41–78)	66 (57–75)	67 (55–72)	70 (30–77)	.908
Sex (male/female), *n*	11/4	11/4	5/1	15/6	.766
Bismuth type (I–III / IV), *n*	6/9	7/8	3/3	6/15	.272
CA19-9, U/mL (range)	516 (1–14,240)	396 (16–219,784)	2,583 (24–15,683)	232 (1–18,150)	.243
Carcinoembryonic antigen, ng/mL (range)	4.2 (1–28.5)	3.1 (1.8–19.1)	4.2 (1.7–18.4)	4.1 (0.5–131.6)	.734
No. of liver metastasis detected by preoperative CT, *n* (range)	4 (1–10)	0	1.5 (0 –10)	0	—
No. of liver metastasis detected at laparotomy, *n* (range)	—	1 (1–10)	1.5 (1–10)	0	—
No. of liver metastasis detected by final pathology, *n* (range)	—	—	1.5 (1–15)	1 (1–6)	—
Location of liver metastasis (unilobar/bilobar), *n*	8/7	14/1	5/1	19/2	.185
Diameter of liver metastasis, mm (range)†	14 (7–26)	9 (2–40)	13 (6–25)	5 (1–12)	<.001

Group A, inoperable patients owing to liver metastasis detected by preoperative work up; *Group B*, explored by laparotomy but unresected patients owing to liver metastasis detected by intraoperative inspection; *Group C*, hepatectomized patients with overt liver metastasis; *Group D*, hepatectomized patients with occult liver metastasis (Fig 3).
Continuous data were expressed as median (range).
* Indicating the difference between overt (groups A–C) and occult (group D) metastases.
† Diameter of the largest metastasis in case of multiple metastases.

external surface of the liver. The diameters of occult liver metastases (the largest one when multiple) was ≤3 mm in 9 patients, 4 mm to 10 mm in 11 patients, and 12 mm in one patient, with a median diameter of 5 mm.

When compared between the overt liver metastases (groups A, B, and C) and the occult liver metastases (group D; Table I), no between-group differences were observed in age, sex, Bismuth type, tumor marker, and location of the liver metastases. Conversely, the diameters of liver metastases were smaller in the occult metastasis groups than in the overt metastasis groups (5 mm vs 12 mm, $P < .001$).

Next, the 21 resected patients with occult liver metastases were compared with the 645 resected patients without synchronous liver metastases (Table II). A Bismuth type IV tumor was prevalent in the former than in the latter. Microscopic venous invasion, microscopic liver invasion, and lymph node metastases were also observed more frequently in the former than in the latter. As anticipated, the patients with occult liver metastases had more advanced stages of the disease.

Survival

In groups C and D, 90-day mortality after hepatectomy was 0%, and it was 2.0% (13 out of 645) in group E. Survivals were compared among the 5 patient groups (groups A–E, Fig 3). Survivals for the group A, B, and C patients were almost identical and uniformly

Table II
Comparison between patients with occult liver metastasis and those without liver metastasis

Variables	Occult liver metastasis (group D*)	No liver metastasis (group E*)	*P* value
No. of patients, *n*	21	645	—
Age, y (range)	70 (30–77)	68 (31–89)	.370
Sex, *n* (%)			.645
Male	15 (71.4)	416 (64.5)	
Female	6 (28.6)	229 (35.5)	
Body mass index, kg/m^2 (range)	21.4 (16.0–30.8)	21.3 (13.1–35.2)	.452
CA19-9, U/mL (range)	232 (1–18,150)	81 (1–52,831)	.163
Carcinoembryonic antigen, ng/mL (range)	4.1 (0.5–131.6)	2.3 (0.3–174.0)	.054
Bismuth classification, *n* (%)			.024
1, 2, 3	6 (28.6)	360 (55.8)	
4	15 (71.4)	285 (44.2)	
Extent of liver resection, *n* (%)			
<50%	7 (33.3)	214 (33.2)	.999
≥50%	14 (66.7)	431 (66.8)	
Combined vascular resection, *n* (%)	11 (52.4)	268 (41.6)	.373
Operative time, min (range)	595 (459–845)	600 (344–1,150)	.643
Blood loss, mL (range)	1,161 (370–3,423)	1,333 (46–11,115)	.631
Histopathologic classification, *n* (%)			.037
Well	1 (4.8)	167 (25.9)	
Moderately/poorly/others	20 (95.2)	478 (74.1)	
Microscopic lymphatic invasion, *n* (%)	18 (85.7)	461 (71.5)	.217
Microscopic venous invasion, *n* (%)	17 (81.0)	300 (46.5)	.003
Microscopic perineural invasion, *n* (%)	19 (90.5)	550 (85.3)	.754
Microscopic liver invasion, *n* (%)	19 (90.5)	392 (60.8)	.005
Pathological tumor category, *n* (%)			.010
is 1/2	2 (9.5)	239 (37.0)	
3/4	19 (90.5)	406 (63.0)	
Lymph node metastasis, *n* (%)	16 (76.2)	303 (47.0)	.013
R1 resection, *n* (%)	6 (28.6)	134 (20.8)	.415
90-day mortality, *n* (%)	0	13 (2.0)	.999

Continuous data were expressed as median (range).
* See Fig 3.

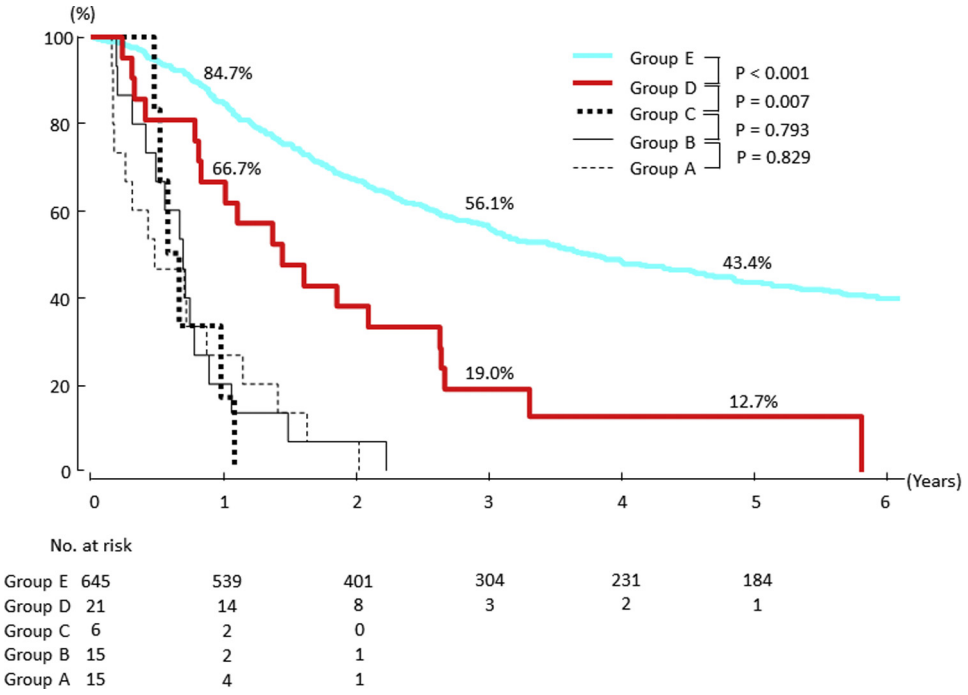

Fig 4. Survival curves for patients with or without liver metastases. *Group A*, inoperable patients owing to liver metastases detected by preoperative workup; *group B*, patients operated, but unresected patients owing to liver metastases detected by intraoperative inspection; *group C*, hepatectomized patients with overt liver metastases; *group D*, hepatectomized patients with occult liver metastases; *group E*, hepatectomized patients without liver metastases (Fig 3).

dismal; most of the patients died of the disease within 2 years. In contrast, although survival for group D patients was worse than that for group E patients, the survival was better than those for group A, B, and C patients (Fig 4). The median survival time was 7.4 months in groups A to C, 17.1 months in group D, and 45.2 months in group E.

Of the 21 group D patients, 15 had single, occult metastases, and the remaining 6 had multiple occult metastases; their survivals were almost identical (median survival time 19.6 vs 16.7 months, $P = .789$). Eleven patients, most of whom underwent operation after 2007, received adjuvant chemotherapy, and their survival was better than that of the remaining 10 patients without adjuvant chemotherapy (median survival time 25.5 vs 10.0 months, $P = .008$). At the time of this writing, 19 patients had died of recurrence, including liver ($n = 14$), peritoneum ($n = 8$), lung ($n = 4$), locoregional ($n = 3$), brain ($n = 1$), and bone ($n = 1$) recurrences, with some overlap. The remaining 2 patients are still alive without recurrence for 47 and 33 months, respectively.

Prognostic factors in patients with occult liver metastasis

Prognostic factors in the 21 patients with occult liver metastasis were analyzed. Of these, 11 patients underwent adjuvant chemotherapy, and the remaining 10 patients did not. The regimens used were gemcitabine hydrochloride ($n = 5$), S-1 ($n = 5$), and gemcitabine with cisplatin ($n = 1$). The reasons for the lack of adjuvant chemotherapy in the remaining 10 patients were because the operations were done before 2007 ($n = 6$), refusal by patients themselves ($n = 3$), and unknown causes ($n = 1$).

On univariate analysis, 2 of 9 possible clinicopathologic prognostic factors were statistically significant (Table III). Multivariate analysis using these factors revealed that adjuvant chemotherapy and lymph node metastasis appeared to be independent prognostic factors in patients with occult liver metastasis.

Discussion

The present study is the first report on occult synchronous liver metastases from PHCC, which are defined as intrahepatic metastases that are overlooked by preoperative diagnostic imaging and intraoperative inspection but that are detected by final pathology. Under the definition, such liver metastases were observed in 3.1% (21 out of 672) of hepatectomized patients. This incidence was low, but not extremely rare and was greater than we anticipated. Strictly speaking, because only resected segments of the liver were examined histologically, it is unclear whether occult liver metastases existed in the remnant liver or not. In addition, if the specimens were cut into more fine sections (3 mm intervals), the incidence may have increased. Thus, the incidence is at least 3.1%. Occult liver metastases could be identified, because hepatectomy had been performed as a resectional procedure. These metastases, if any, have never been detected in other gastrointestinal malignancies in which hepatectomy is not necessary for curative resection. Consequently, the term occult synchronous liver metastasis can be applied specifically only for hepatobiliary malignancies that require a hepatectomy or a liver transplantation.

Recently, Aufhauser et al investigated the incidence of radiologically unrecognized (occult) intrahepatic metastases in explant hepatectomy specimens from orthotopic liver transplants for hepatocellular carcinoma.[9] Even in patients having a single tumor with model of end-stage liver disease score $\leq$10, occult multifocality was found in as many as 35 % (452 out of 1287) of the patients, with a median number of 1 (range, 1–5). Compared with this result, the incidence in the present study was much less, although biologic behaviors and surgical procedures are largely different between PHCC and hepatocellular carcinoma.

The present study has shown that thorough investigations of the resected specimens are important in detecting occult liver metastases. As mentioned in the Methods section, all of the resected specimens were subjected routinely to serial sectioning at 5-mm

Table III
Univariate and multivariate analyses for prognostic factors in patients with occult liver metastasis

Variables	n	Median survival time (mo)	Univariate	Multivariate	
			P value	HR (95% CI)	*P* value
Age			.257		
<70 y	10	17.6			
≥70 y	11	10.0			
Sex			.443		
Male	15	16.7			
Female	6	17.6			
CA19-9			.781		
<100 IU/L	8	17.6			
≥100 IU/L	13	15.4			
Extent of liver resection			.296		
<50%	7	6.0			
	1				
≥50%	14	17.6			
Blood loss			.422		
<1,200 mL	11	19.6			
≥1,200 mL	10	12.4			
No. of occult liver metastasis			.789		
Single	15	19.6			
Multiple	6	16.7			
Lymph node metastasis			.019		.045
Absent	5	70.0		1	
Present	16	12.4		3.41 (1.19–9.83)	
R status (curability)			.470		
R0	15	17.6			
R1	6	10.0			
Adjuvant therapy			.008		.023
Absent	10	10.0		1	
Present	11	25.5		0.21 (0.04 − 0.97)	

intervals, after 10% formalin fixation.[6] Also, we carefully inspected the cut surfaces of the resected specimens with attention paid to small nodules that were suspected to be liver metastases. When such lesions were found on the cut surfaces, they were investigated histologically. The 21 patients with occult liver metastases were eventually categorized as having a stage IVB cancer because a liver metastasis is defined as a pM1 disease.[7] If occult liver metastases were not found, then they would be categorized into other stages. Meticulous handling of the resected specimens with careful gross and histologic inspection is crucial to detect these small, intrahepatic metastases, which will then lead to more accurate tumor staging.

Preoperative diagnoses of liver metastases in the present series were unexpectedly poor. Of the 57 patients with liver metastases including occult metastases, only 20 (35.1%) patients were diagnosed definitively with liver metastases using preoperative CT. In the remaining 37 patients, metastases were never detected or, if detected, they presented as small, space-occupying lesions, thus resulting in nondefinitive diagnoses. One possible reason is that few patients with PHCC underwent MRI as part of the preoperative workup owing to our institutional strategy. Specifically, no patients with liver metastases underwent MRI. Although it may have been difficult to detect occult liver metastases even with MRI, improvement of the diagnostic accuracy for liver metastases is an important task.

We purposely performed a hepatectomy in 6 selected patients with overt metastases with the expectation that hepatectomy might improve their qualities of life; all of the patients, however, died of their disease within 2 years, and their survival curve was almost identical to that for the unresected patients. These findings clearly suggest that patients with PHCC and overt liver metastases are beyond any reasonable indication for resection. These excessive hepatectomies were performed in the early 2000s, and thereafter, we no longer perform such resections.

In the resected patients with occult liver metastases, the survival was significantly better than that in the patients with overt liver metastasis. Actually, 8 patients with occult liver metastasis survived for >2 years, whereas almost all patients with overt metastasis died within 2 years. This noticeable finding may be attributed primarily to lead time bias, meaning that the patients with occult liver metastasis are earlier in their timeline of disease progression. In contrast, multivariate analysis revealed that the adjuvant chemotherapy is an independent prognostic factor. The survival of the 10 patients without adjuvant chemotherapy was dismal, being similar to that of groups A to C (Table III). Thus, a possibility may also exist that adjuvant chemotherapy using gemcitabine or S-1[10–12] is somewhat effective for the treatment of occult liver metastasis. Regardless, because the number of analyzed patients is limited, further studies are needed. At present, we use S-1 routinely as adjuvant chemotherapy for resected patients with lymph node metastasis, R1 resections, and occult liver metastasis. Because S-1 is an oral drag, it is much easier to use as adjuvant chemotherapy. Adjuvant radiotherapy is also used in patients with R1 resection according to surgeon's preference.

The present study has some limitations, including its retrospective nature and the data of a single center; therefore, unexpected biases cannot be completely excluded. The small number of patients with occult liver metastasis is also a limitation; however, owing to the rarity and lack of awareness about this metastasis, conducting a study with a large sample size will be very difficult. Nevertheless, the present study comprises one of the largest series of patients with PHCC and is the first report on this issue. Another limitation of this study is the lack of using a preoperative MRI for staging and the lack of using intraoperative ultrasonography to look for these occult liver metastatses both in the resected liver and in the remnant liver; use of these techniques may have changed our planned treatment and will need to be evaluated in the future. In Japan, most surgeons have traditionally preferred CT rather than MRI.[5] In contrast, MRI has been used widely in Western countries[1–4]; therefore, studies from such countries are expected. A more routine use of intraoperative ultrasonography will need to be considered seriously in out practice.

In conclusion, occult liver metastases from PHCC are not extremely rare (≈3%). Meticulous handling of the resected specimen as presented here is important to detect such metastases and leads to more accurate tumor staging. Patients with occult liver metastasis have advanced stages of the disease; however, their survival may be improved by the use of adjuvant chemotherapy.

Disclosure

The present authors declare no conflict of interest.

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"Oh, it's a stethoscope. I just wear it to show I'm a doctor. I don't use it."