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Pleural dissemination of cholangiocarcinoma caused by percutaneous transhepatic biliary drainage during the management of resectable cholangiocarcinoma

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ABSTRACT

Background: Only 3 case reports have addressed pleural dissemination in association with percutaneous transhepatic biliary drainage. The aim of this study was to investigate recurrence after resection of cholangiocarcinoma after percutaneous transhepatic biliary drainage and to clarify the incidence of and the factors responsible for pleural dissemination.

Methods: Between 2001 and 2015, we reviewed retrospectively all consecutive patients who underwent resection for perihilar or distal cholangiocarcinoma after percutaneous transhepatic biliary drainage for recurrence, including pleural dissemination.

Results: During the study period, all consecutive patients underwent resection of cholangiocarcinoma after management with percutaneous transhepatic biliary drainage. Of these, 100 patients (32.1%) underwent left-sided percutaneous transhepatic biliary drainage alone, and 212 (67.9%) underwent right-sided percutaneous transhepatic biliary drainage with or without left-sided percutaneous transhepatic biliary drainage. Pleural dissemination, which developed exclusively on the right side of the thoracic cavity after resection, was found in 12 patients (3.8%); these patients underwent right-sided percutaneous transhepatic biliary drainage; computed tomography demonstrated that the percutaneous transhepatic biliary drainage catheter passed through the thoracic cavity in all 12 patients. The diagnosis of pleural dissemination was made at a median of 381 days (range, 44 to 2,944 days) after operation. Survival was poor, with a median survival time of 516 days. Statistically, right-sided percutaneous transhepatic biliary drainage was identified as a risk factor for pleural dissemination.

Conclusion: Pleural dissemination after right-sided percutaneous transhepatic biliary drainage is likely a procedure-related iatrogenic complication because of the “special route” by which the percutaneous transhepatic biliary drainage catheter must be passed through the right thoracic cavity.

Introduction

Percutaneous transhepatic biliary drainage (PTBD) has been used widely as an established biliary drainage method for malignant obstructions.[1–4] The potential of metastatic seeding along the track of the PTBD catheter is a serious problem associated with this intervention. Several authors have reported that PTBD increases the incidence of metastatic seeding and decreases the survival of these patients with resectable cholangiocarcinoma[5–11] or pancreas ductal adenocarcinoma.[12,13] The oncologic inferiority of PTBD compared with endoscopic drainage is now becoming evident.

Peritoneal dissemination and sinus tract recurrence are well-known typical manifestations of metastatic seeding associated with PTBD,[5–11] but little is known about pleural seeding after PTBD. To our knowledge, only 3 case reports have addressed pleural seeding as a rare complication after PTBD.[14–16]

The aim of this retrospective study was to investigate pleural recurrence after resection of cholangiocarcinoma after PTBD and to clarify the incidence of and factors responsible for pleural seeding after PTBD.

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Methods

Study patients

Between 2001 and 2015, all consecutive patients who underwent resection for perihilar or distal cholangiocarcinoma after PTBD at the First Department of Surgery, Nagoya University Hospital, were reviewed retrospectively from a prospectively maintained database, and recurrence including pleural dissemination was noted. This study was approved by the Human Research Review Committee of Nagoya University Hospital (approval number 2017-0319).

Preoperative management

As part of the preoperative workup, cholangiography and multidetector-row computed tomography (MDCT) were performed routinely in all patients. PTBD was performed with Takada's direct anterior approach under fluoroscopic control[1–3] or with ultrasonographic guidance. Multiple PTBDs were performed when needed, primarily in patients with Bismuth type III or IV tumors. Usually, the tip of the PTBD catheter was positoned transtumorally into the common bile duct. All of the bile drained externally was replaced orally or via a nasoduodenal tube to maintain the intestinal mucosal integrity, as reported previously.[17] No patients received neoadjuvant chemotherapy.

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For distal cholangiocarcinoma, pancreatoduodenectomy was performed. For hilar cholangiocarcinoma, the type of hepatectomy was determined based on the location of the primary tumor, as reported previously.[18] The pathologic findings of resected specimens were documented prospectively according to the 7th edition of the American Joint Committee on Cancer Staging Manual.

Follow-up of patients who underwent resection

Physical examination and blood tests, including tumor markers, were performed every 2 to 3 months. MDCT was undertaken at least twice a year for the first 5 years. As adjuvant treatment, Gemzar® (Gemcitabine hydrochloride, Eli Lilly and Company, Indianapolis, IN) or TS-1® (Tegafur-Gimeracil-Oteracil potassium, Taiho Pharmaceutical Co Ltd, Tokyo, Japan) was used, mainly in patients with lymph node metastases who were treated after 2007 because these agents were authorized for use in 2007. Radiation therapy was also used in patients with positive surgical margins.

Definition of recurrence

Recurrence was diagnosed on the basis of radiologic and/or cytologic findings. Even if the tumor markers were increased to levels greater than the normal limits, a diagnosis of recurrence was not made before the radiologic or cytologic evidence had been reviewed. Recurrence in the PTBD sinus tract was defined as a cutaneous tumor at the PTBD scar site or an abdominal/thoracic wall tumor situated along the PTBD sinus tract.[5–7] Peritoneal or pleural dissemination was confirmed by progressive fluid accumulation and radiologic evidence of a tumor nodule or fluid cytologic evidence of cancer cells.

Statistical analysis

The results are expressed as median values with ranges unless otherwise specified. The statistical analysis was performed using χ^2 test or Fisher probability test for categorical variables. To evaluate the risk factors for pleural dissemination after PTBD, the Mantel-Haenszel test was performed across strata for covariates that had a $P < .25$ in a univariate Fisher probability test. Postoperative survival was calculated using the Kaplan-Meier method, and differences in the survival curves were compared using the log-rank test. Analyses were performed using the SPSS version 22 (IBM Japan, Tokyo, Japan).

Table 1
Number of PTBD procedures and puncture site in all study patients.

Number of PTBD			Number of patients
Total	Right side	Left side	
1	1	0	82
1	0	1	93
2	1	1	55
2	2	0	28
2	0	2	7
3	3	0	7
3	2	1	20
3	1	2	7
4	3	1	2
4	2	2	7
4	1	3	2
5	3	2	2

Results

Patient demographics

During the study period, all consecutive patients underwent resection of distal ($n = 28$) or perihilar ($n = 284$) cholangiocarcinoma after management with PTBD. They were reviewed in the present study, including 197 men and 115 women with a median age of 66 years (range, 30 to 85 years).

The operations performed in the all patients were hepatectomy with extrahepatic bile duct resection ($n = 234$), pancreatoduodenectomy ($n = 28$), hepatopancreatoduodenectomy[19] ($n = 44$), and extrahepatic bile duct resection alone ($n = 6$). There were no patients in whom the right diaphragm was opened intraoperatively.

Number of PTBD procedures and puncture site

The number of PTBD procedures and puncture sites are summarized in Table 1. The duration of management with PTBD was 39 days (range, 7 to 376 days). Of the all patients, 137 (43.9 %) patients underwent multiple PTBD procedures. In terms of the puncture sites for PTBD, 100 (32.1%) patients underwent left-sided PTBD alone, another 117 (37.5%) underwent right-sided PTBD alone, and the remaining 95 (30.4%) underwent bilateral PTBD. Overall, 212 (67.9%) patients underwent right-sided PTBD with or without left-sided PTBD. All of the right-sided PTBD were performed via the intercostal route.

Pleural dissemination

Pleural dissemination which developed exclusively on the right side of the thoracic cavity was found in 12 (3.8%) of the all patients (Fig. 1). All 12 patients underwent right-sided PTBD with ($n = 5$) or without ($n = 7$) left-sided PTBD. MDCT demonstrated that the PTBD catheter passed through the right thoracic cavity in all 12 patients (Fig. 2). The clinicopathologic details of the 12 patients are shown in Table 2.

The diagnosis of pleural dissemination was made at a median of 381 days (range, 44–2944 days) after operation. In 7 of the 12 patients, pleural dissemination with or without other sites of recurrence was the initial site of recurrence. In the remaining 5

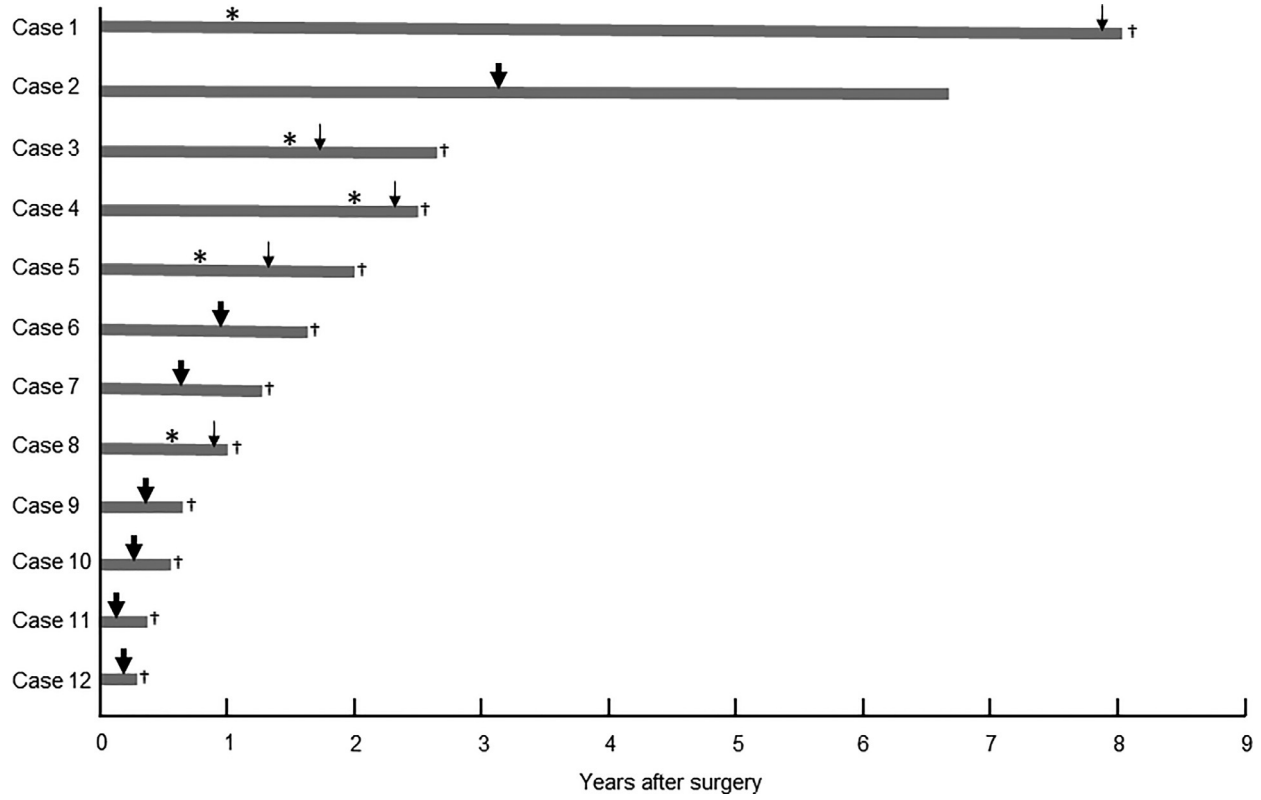

Fig. 1. Postoperative follow-up of the 12 patients with pleural dissemination. Bold arrow, diagnosis of pleural dissemination as the initial recurrence, with or without other recurrence. Fine arrow, diagnosis of pleural dissemination as the second recurrence.
*diagnosis of an initial recurrence other than pleural dissemination.
†died of the disease.

Table 2
Details of the 12 patients with pleural dissemination.

Case #	Age	Sex	PTBD			Morphologic tumor type	Primary tumor location	Operative procedure*	Other seeding metastasis	
			Number	Puncture site	Duration (days)				Peritoneal recurrence	PTBD tract recurrence
1	57	Male	5	Rt & Lt	42	Infiltrating	Hilar	S1,4,5,6,7,8 + PV	+	–
2	72	Male	2	Rt	99	Papillary	Hilar	S1,5,6,7,8	–	+
3	55	Male	2	Rt & Lt	28	Infiltrating	Hilar	S1,2,3,4 + PV	+	–
4	70	Male	3	Rt & Lt	72	Nodular	Hilar	S1,2,3,4	+	+
5	72	Male	2	Rt & Lt	25	Nodular	Hilar	S1,2,3,4 + PV	+	–
6	54	Male	1	Rt	22	Nodular	Hilar	S1,2,3,4,5,8	–	–
7	70	Male	1	Rt	50	Nodular	Distal	S1,5,6,7,8 + PD + PV	+	–
8	57	Male	1	Rt	33	Nodular	Hilar	S,1,2,3,4	–	–
9	63	Male	1	Rt	47	Nodular	Distal	PD	+	–
10	71	Female	1	Rt	19	Infiltrating	Hilar	S1,5,6,7,8 + PV	–	–
11	75	Male	1	Rt	20	Nodular	Hilar	S1,5,6,7,8	–	–
12	71	Male	2	Rt & Lt	94	Nodular	Hilar	S1,2,3,4	–	–

PV = portal vein resection; PD = pancreatoduodenectomy.
* Expressed as Couinaud's hepatic segments resected.

patients, pleural dissemination was detected as the second site of recurrence. Most of the patients with pleural dissemination died within 3 years; their median survival time was only 516 days. In the 231 patients with recurrence after the original operation, survivals were similar between the 12 patients with pleural dissemination and the remaining 219 patients without pleural dissemination (median survival time; 516 days vs 594 days, $P = .919$).

Peritoneal and PTBD sinus tract recurrence

The incidences of peritoneal recurrence and PTBD sinus tract recurrence were also investigated as other potential sites of metastatic seeding. Peritoneal recurrence was found in 91 (29.2%) of the patients, and its incidence was similar irrespective of puncture site (right-sided alone, 29.9% = 35/117; left-sided alone, 25.0% = 25/100; bilateral, 32.6% = 31/95: $P = .491$). Median survival time of the 91 patients with peritoneal recurrence was 409 days.

PTBD sinus tract recurrence was observed in 15 (4.8%) of the cohort. Right-sided tract recurrence was found in 9 (4.2%) of the 212 patients who underwent right-sided PTBD with or without left-sided PTBD. In contrast, left-sided tract recurrence was found in 6 (3.1%) of the 195 patients who underwent left-sided PTBD with

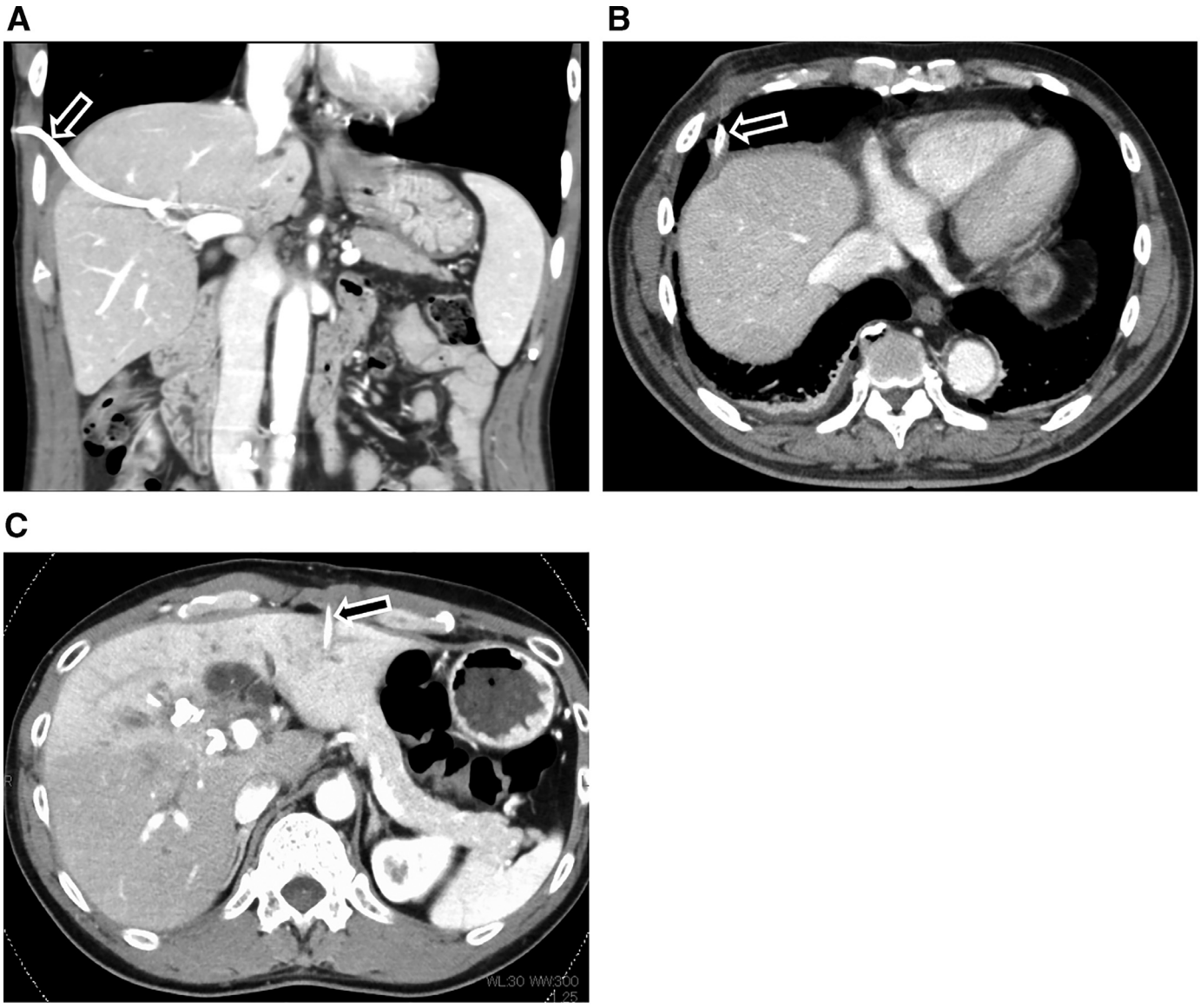

Fig. 2. Computed tomography findings. *A,* Percutaneous transhepatic biliary drainage (PTBD) catheter (arrow) is passed through the right side of the thoracic cavity from the right flank. *B,* PTBD catheter (arrow) is passed through the right side of the thoracic cavity from the right precordium. *C,* During left-sided PTBD, a PTBD catheter (arrow) is never passed through the left side of the thoracic cavity.

or without right-sided PTBD. These incidences were not different ($P = 0.605$).

The relation among 3 types of metastatic seeding, i.e., pleural recurrence, peritoneal recurrence, and PTBD sinus tract recurrence, is described in Fig. 3.

Risk factors for pleural dissemination

To identify the risk factors for pleural dissemination, 18 clinicopathologic variables were investigated. In the univariable analyses, only the puncture site for PTBD was statistically significant (Table 3). Logistic regression analysis could not be performed owing to presence of cells with a value of 0. To further validate the risk factors, therefore, the Mantel-Haenszel test was performed using 3 variables with $P < .25$ in the univariable analysis. The puncture site of PTBD and sex were confirmed to be significant risk factors ($P = .014$ and $P = .042$, respectively), but blood loss was not ($P = .346$).

Discussion

The present study demonstrated the following: first, the incidence of pleural dissemination was 3.8% in patients who underwent resection of cholangiocarcinoma after management preoperatively with PTBD. This incidence was not extremely rare and was greater than we anticipated; second, all instances of pleural disseminations were found on the right side of the thoracic cavity; and third, all of the patients with pleural dissemination underwent right-sided PTBD before operation. According to the univariable analysis and Mantel-Haenszel test, right-sided PTBD was identified as a risk factor for pleural dissemination. Sex of the patient was also a significant risk factor, but we speculate that this is incidental without any clinical implication.

Previously, only 3 case reports[14–16] have addressed pleural dissemination after PTBD. The first reported patient[14] presented with obstructive jaundice owing to unresected hilar cholangiocarcinoma and underwent right-sided PTBD; 18 months after the initial PTBD, a large right pleural effusion was noted; thoracentesis showed

Table 3
Univariable analysis of risk factors for pleural dissemination.

Variables	Number of patients	Pleural dissemination (%)	*P*
Age			>.999
<65 years	138	5 (3.6)	
≥65 years	174	7 (4.0)	
Sex			.062
Female	115	1 (0.9)	
Male	197	11 (5.6)	
Puncture site of PTBD			**.011**
Left-sided alone	100	0 (0.0)	
Right-sided or bilateral	212	12 (5.7)	
Number of PTBD			.770
Single	175	6 (3.4)	
Multiple	137	6 (4.4)	
Duration of PTBD			>.999
<40 days	157	6 (3.8)	
≥40 days	155	6 (3.9)	
Preoperative cholangitis			.512
Absent	232	8 (3.4)	
Present	80	4 (5.0)	
Location of tumor			.636
Perihilar	276	10 (3.6)	
Distal	36	2 (5.6)	
Operative time			>.999
<10 h	115	4 (3.5)	
≥10 h	197	8 (4.1)	
Blood loss			.240
<1,500ml	137	3 (2.2)	
≥1,500ml	175	9 (5.1)	
Postoperative bile leakage			.674
Absent	269	10 (3.7)	
Present	43	2 (4.7)	
Histopathologic classification			.701
Well	60	3 (5.0)	
Moderately/Poorly/others	252	9 (3.6)	
Morphologic tumor type			>.999
Papillary type	33	1 (3.0)	
Nodular/infiltrating type	279	11 (3.9)	
Microscopic lymphatic invasion			.740
Absent	72	2 (2.8)	
Present	240	10 (4.2)	
Microscopic venous invasion			.559
Absent	184	6 (3.3)	
Present	128	6 (4.7)	
Microscopic perineural invasion			.370
Absent	39	0 (0.0)	
Present	273	12 (4.4)	
Pathologic tumor category			>.999
is/1/2	94	3 (3.2)	
3/4	218	9 (4.1)	
Lymph node metastasis			.381
Absent	151	4 (2.6)	
Present	161	8 (5.0)	
Surgical margin			.523
R0	227	10 (4.4)	
R1	85	2 (2.4)	

adenocarcinoma. The patient died 4 months later. The second patient[15] also had hilar cholangiocarcinoma and underwent a left hepatectomy with caudate lobectomy after right-sided PTBD; 14 months after the operation, MDCT revealed an effusion and multiple right pleural masses. The patient underwent panpleuropneumonectomy but died of recurrent pleural metastatic disease 9 months after the panpleuropneumonectomy. The third patient[16] underwent a right hepatectomy for hilar cholangiocarcinoma after right-sided PTBD; 18 months postoperatively, a small right pleural metastasis was found. Chemoradiation therapy was not effective, and the patient died of pleural dissemination 18 months later (36 months after the initial operation).

The findings of the current study and the previous 3 case reports[14–16] suggest strongly that pleural dissemination after right-sided PTBD is a procedure-related complication owing to the "special transthoracic route" which the PTBD catheter must take through the right side of the thoracic cavity. In contrast, we experienced a patient who had undergone resection of hilar cholangiocarcinoma after endoscopic drainage and who developed right-sided pleural dissemination 18 months after hepatectomy. Furthermore, in the first case in the present series (Fig. 1), pleural dissemination was detected more than 7 years after the resection of the cholangiocarcinoma; thus, this recurrence may not have been related to PTBD. In short, most but not all of the instances of right-sided pleural dissemination after right-sided PTBD are late iatrogenic complications related to PTBD.

Considering the increased risk of metastatic seeding related to PTBD,[5–13] endoscopic biliary drainage has become popular in Japan. The Japan Clinical Practice Guidelines for Biliary Tract Cancer[20] strongly recommend the use of endoscopic drainage and not PTBD as the method of choice for preoperative biliary drainage. In contrast, PTBD is still used widely in some Western and

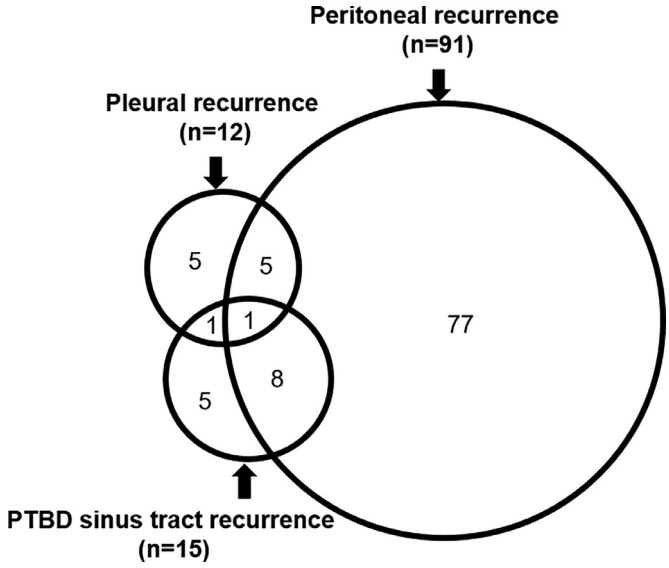

Fig. 3. Relation among 3 types of seeding metastasis, including peritoneal recurrence, pleural recurrence, and percutaneous transhepatic biliary drainage (PTBD) sinus tract recurrence.

Eastern countries.[21–23] Thus, doctors who prefer PTBD should be aware of the risk of PTBD-related pleural dissemination, and left-sided puncture should be performed, if possible, to circumvent this serious iatrogenic complication. The frequent exchange of the PTBD catheters and manipulation of the tumor by inserting the catheter through the tumor are considered the main causes of seeding along the catheter tract. Thus, these procedures should also be avoided whenever possible. The complications associated with traversing the pleural space during PTBD have been well documented and include pneumothorax, hemothorax, empyema, and biliary pleural fistula.[24,25] Some authors have mentioned that these complications can be avoided by careful delineation of the pleural recess and entry below the tenth rib, but this may be difficult to perform.

The main limitation of this study was its retrospective nature, the small number of patients with pleural dissemination, and the fact that it was a single-center study. Because of the rarity and lack of awareness about this complication, conducting a study with a large sample size will be difficult. Despite some limitations of this study, we believe that the data and the conclusions presented here are reasonable and convincing. Further studies from centers where PTBD is currently used are expected.

Conclusion

Pleural dissemination after right-sided PTBD is likely a procedure-related iatrogenic complication owing to the “special transthoracic route” by which the PTBD catheter must pass to puncture the liver for retrograde percutaneous biliary drainage. Thus, left-sided puncture, if possible, is recommended to circumvent this serious iatrogenic complication.

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