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（大川伸一）

胆・膵

ソナゾイド®（Sonazoid®）での二次元または三次元造影超音波はレボビスト®（Levovist®）よりも造影剤の泡が壊れにくいため病変全体の詳細な血行動態（腫瘍血管と腫瘍濃染）の観察が可能であり，膵腫瘍と胆嚢病変の質的診断と病変の広がりの診断に有用である。

沼田和司　杉森一哉　森本　学　大西奈緒美　田中克明

ハーモニックイメージによる造影超音波は空間分解能に優れ，膵腫瘤や胆嚢病変の血行動態をリアルタイムに観察可能である[1~5]。新規超音波造影剤であるソナゾイド®は低音圧で撮影することを推奨されているが，現時点での低音圧用造影ソフトでは病変の血管以外の組織の輝度が高い場合，組織と血管の信号をきれいに分離できず，詳細な腫瘍血管の観察が困難な場合がある。造影剤を注入後，腫瘍血管と腫瘍濃染を観察するには，血管以外の組織からの高調波信号を抑えて血管からの高調波信号を増強するために，主に高音圧用の造影ソフトであるcoded harmonic angio（CHA）モードを用いて観察した。それによってリアルタイムに腫瘍血管，腫瘍濃染を観察可能であった。またソナゾイド®での造影はレボビスト®に比較して気泡が壊れにくいために，三次元造影超音波での撮影で腫瘍全体の観察も可能になった。今回われわれは膵腫瘍と胆嚢病変に対して，ソナゾイド®造影超音波を施行し，その有用性に関して検討した。

対象と方法

❋ 対象

組織学的もしくは臨床的に診断された，黄色性肉芽腫性胆嚢炎1例，胆嚢腺筋腫症と炎症性ポリープの合併1例，胆嚢癌5例（うち胆泥との合併1例，胆石との合併2例），コレステロールポリープ3例，胆泥のみ3例，膵臓癌18例（うち膵全体癌1例），膵内分泌腫瘍1例，自己免疫性膵炎1例。

❋ 撮影方法

超音波装置はGE社製LOGIQ 7，通常（二次元）の場合は3.5-MHzコンベックスプローブ，三次元の場合はリアルタイム3Dプローブを用いて造影した。二次元の場合はソナゾイド®（0.2ml/body）をbolus injectionし，注入後約60秒までは腫瘍血管と腫瘍濃染をCHAモードの高音圧（MI 約0.8），frame rate 2～7回/秒（通常7回/秒）で観察し（早期相），120秒前後で腫瘍濃染の様子をCHAモードの高音圧，frame rate 2回/秒で観察し（中間相），さらに300秒以降（晩期相）にcoded phase inversion（CPI）モードでの低音圧（MI 約0.2，frame rate 8）で肝全体を観察した後，さらにCHAモードの高音圧，frame rate 2～8回/秒で観察し，肝転移の有無を観察した。三次元の場合は造影剤投与前に腫瘍サイズに合わせてのスキャン角度を決定し（45～70°），上記と同じ量の造影剤を投与し，それぞれの時相でCHAモードの高音圧（MI 約0.6～0.9，frame rate 8）で撮影した。装置内部のコンピュータを使用して三次元再構築し，腫瘍血管と腫瘍濃染を前後方向（A面），左右方向（B面），上下方向

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 0911-1069/08/¥400/論文/JCLS

(C面)に等間隔に並べ評価をした。最後に肝臓全体を二次元もしくは三次元で撮影し，肝転移や肝浸潤の有無を観察した。

造影超音波所見

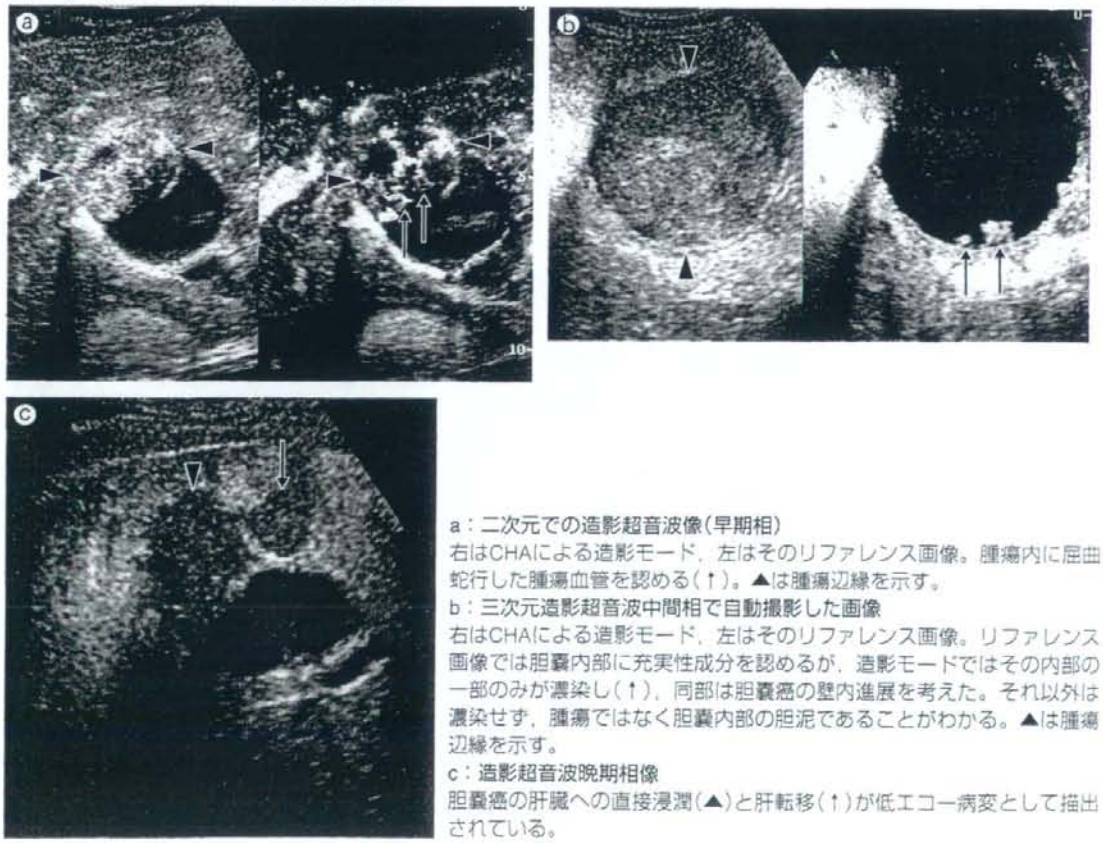
❋ 胆嚢病変

胆嚢病変では胆泥もしくは結石は濃染しないため，それ以外の胆嚢隆起性病変との鑑別が容易に可能であった。それ以外の胆嚢隆起性病変では程度の差こそあれ腫瘍全体が濃染したため，濃染の有無のみでは良・悪性の鑑別はきわめて困難であった。レボビスト®造影同様，腫瘍血管の性状の観察が良・悪性の鑑別に有効と考えた[5]。すなわち，点状または樹枝状の場合は良性の腫瘍，屈曲蛇行した腫瘍血管の場合は胆嚢癌であった。また三次元造影超音波での観察が胆嚢内の病変の広がりと，肝臓への浸潤の評価に有用であった(図1)。一方，黄色性肉芽腫性胆嚢炎症例では中間相，晩期相で肝臓への微小な陰影欠損像があったが，術前にそれが癌によるものか炎症によるものかの鑑別は困難であった。炎症でも造影超音波の中間相，晩期相にて，周囲より低いエコーを呈し，浸潤との鑑別が困難であることを覚えておきたい。この場合，経過観察が可能な場合，時間経過に伴う病変の変化の有無が両者の鑑別の助けになると思われる。

❋ 膵腫瘍

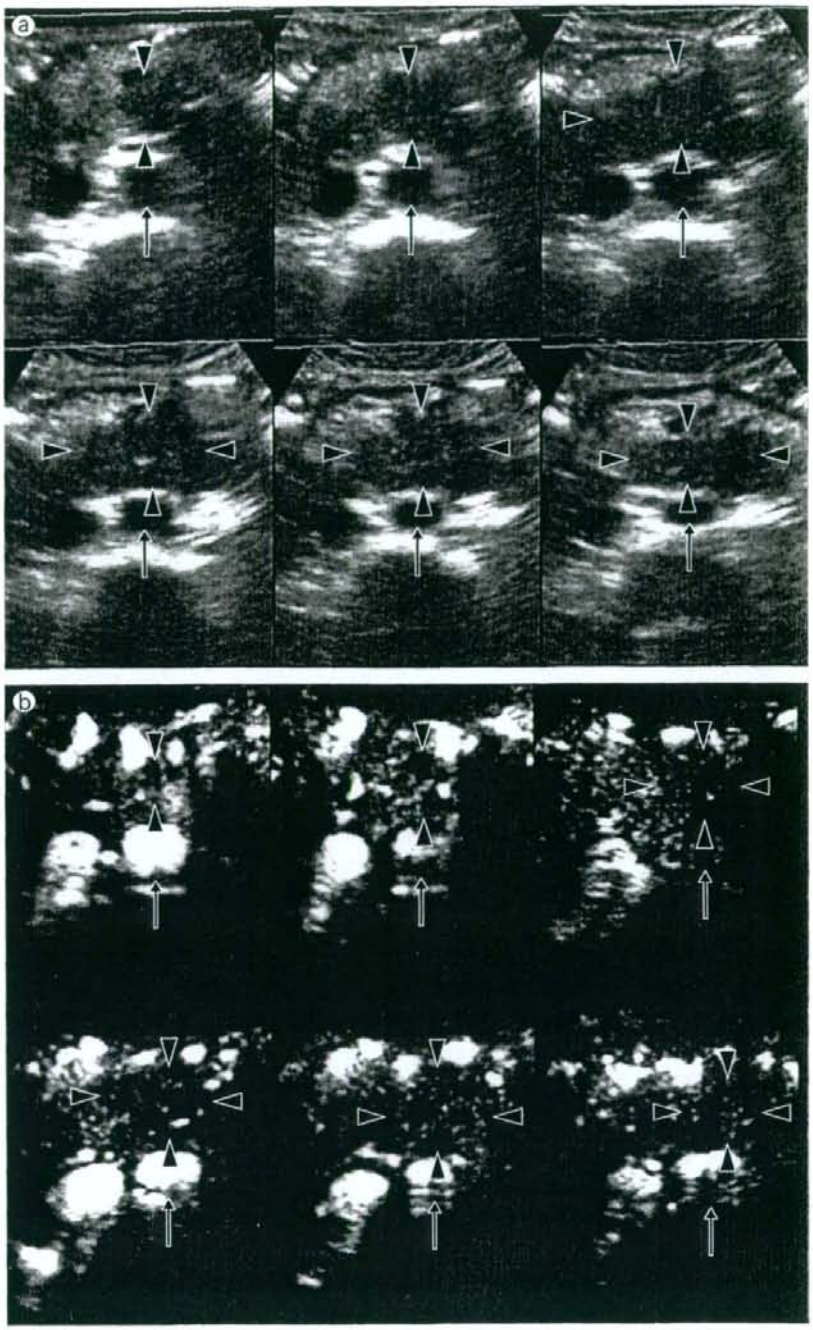
造影超音波は膵腫瘍の鑑別診断に有用であった。すなわち膵内分泌腫瘍では造影早期に腫瘍全体が腫瘍血管と濃染を呈し，自己免疫性膵炎では早期相で腫瘍全体に微細な血管が描出された後，中間相で腫瘍全体が均一に染まった。通常型の膵臓癌18例中16例は辺縁部のみが染まり，内部の染まりが乏しく(図2)，残りの2例は腫瘍全体が染ま

図1　胆嚢癌のソナゾイド®造影超音波像



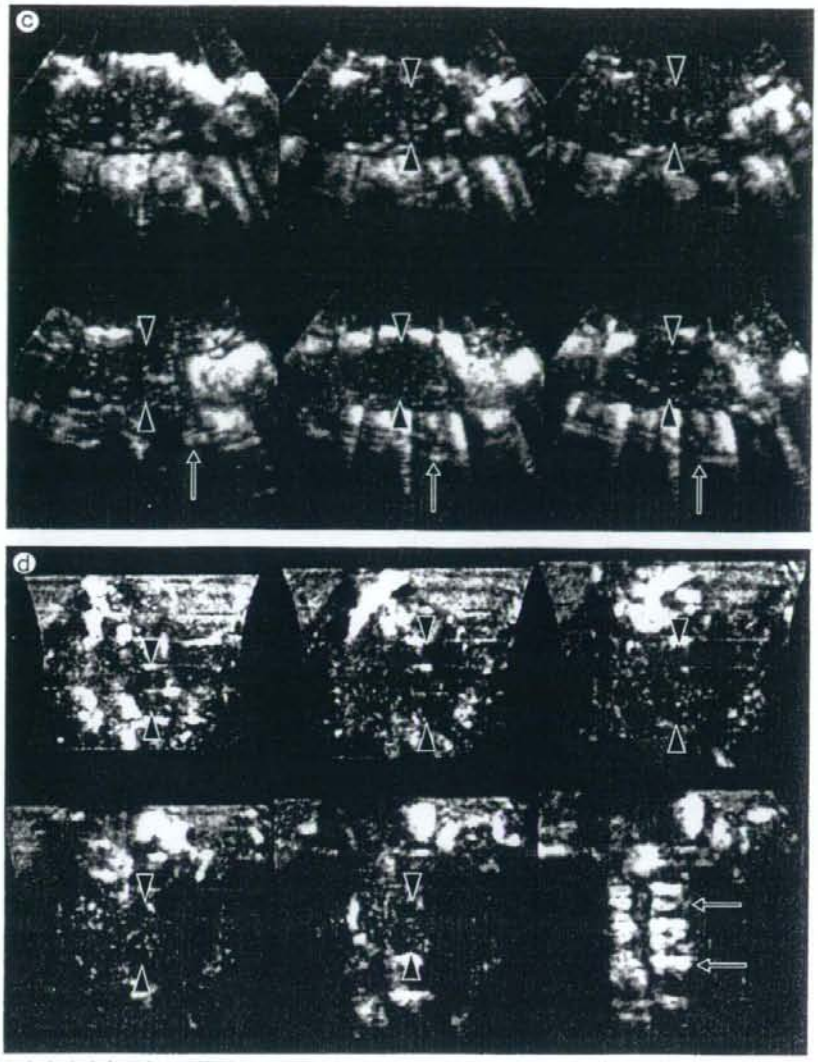
a：二次元での造影超音波像(早期相)
右はCHAによる造影モード，左はそのリファレンス画像。腫瘍内に屈曲蛇行した腫瘍血管を認める(↑)。▲は腫瘍辺縁を示す。
b：三次元造影超音波中間相で自動撮影した画像
右はCHAによる造影モード，左はそのリファレンス画像。リファレンス画像では胆嚢内部に充実性成分を認めるが，造影モードではその内部の一部のみが濃染し(↑)，同部は胆嚢癌の壁内進展を考えた。それ以外は濃染せず，腫瘍ではなく胆嚢内部の胆泥であることがわかる。▲は腫瘍辺縁を示す。
c：造影超音波晩期相像
胆嚢癌の肝臓への直接浸潤(▲)と肝転移(↑)が低エコー病変として描出されている。

図2　膵体部癌のソナゾイド®造影超音波像(a, b)



a：三次元超音波(Bモード)で自動撮影した画像を前後方向(A面)に再構築した画像
膵体部に辺縁不整な低エコー腫瘍を認める(▲)。↑は腹部大動脈を示す。
b：早期相での造影三次元超音波を前後方向(A面)に再構築した画像
腫瘍辺縁部に屈曲した腫瘍血管を認める。腫瘍そのものは周囲の膵実質より染まりが乏しい。▲は腫瘍辺縁，↑は腹部大動脈を示す。

図2　膵体部癌のソナゾイド®造影超音波像(c, d)



c：早期相での造影三次元超音波を左右方向(B面)に再構築した画像
腫瘍辺縁部に屈曲した腫瘍血管を認める。腫瘍そのものは周囲の膵実質より染まりが乏しい。▲は腫瘍辺縁，↑は腹部大動脈を示す。
d：早期相での造影三次元超音波を上下方向(C面)に再構築した画像
腫瘍辺縁部に屈曲した腫瘍血管を認める。腫瘍そのものは周囲の膵実質より染まりが乏しい。▲は腫瘍辺縁，↑は腹部大動脈を示す。

ったが，18例全例，早期相で腫瘍の辺縁部に屈曲した腫瘍血管が存在した。さらに造影超音波では膵周囲の脈管の浸潤の有無，晩期相では肝転移の有無も観察可能であった。特に造影CTでは検出困難な場合がある5mm未満の小転移でも，造影超音波で描出しやすい部位では検出可能であった。さらに三次元造影超音波では1回のスキャンで病変とその周辺の観察が可能であり，膵腫瘍と周辺の膵実質との濃染の差や，膵腫瘍と周囲の脈管との関係，肝転移の有無も観察可能であった。

※ 三次元造影超音波について

リアルタイム三次元プローブとCHAモードでの高音圧でのソナゾイド®造影を組み合わせることで，ボタンを押すと自動的に病変をスキャンし，短時間で造影三次元像を撮影することが可能であ

った。自動スキャンは術者の技量にかかわらず，客観性をもって，胆嚢腫瘍，膵腫瘍の診断を行うことができるが，その際低音圧よりも高音圧で撮影するほうが明瞭な画像を作成することが可能であった。さらにソナゾイド®造影超音波による三次元再構築像を作成し，腫瘍と周囲の脈管との関係を前後，左右，上下と3方向から比較した(図2)。これらの画像をCTやMRIのように等間隔に並べることで，広範囲の病変を1画面でみることができた。その結果，従来の二次元像より客観的に病変を観察することが可能であった。

問題点としては，現時点では前後方向(A面)の空間分解能に比べ，左右方向(B面)，上下方向(C面)の分解能が劣るが，今後の装置の進歩に伴って，これらの方向の空間分解能が改善し，その結果，より正確な診断が可能になることを期待する。

結論

膵腫瘍，胆嚢腫瘍において，二次元造影超音波では腫瘍血管と腫瘍濃染の観察が腫瘍の鑑別診断に有効であった。三次元造影超音波は自動撮影可能なため，一度に広範囲に腫瘍部と非腫瘍部の観察が可能であり，腫瘍血管，腫瘍濃染のみならず，病変の広がりの観察に適していた。今後装置の進歩により，リアルタイムでの三次元像が得られることを期待したい。

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Original Paper

Role of Percutaneous Transhepatic Biliary Drainage in Patients with Obstructive Jaundice Caused by Local Recurrence of Gastric Cancer

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KEY WORDS:
Obstructive jaundice; Percutaneous transhepatic biliary drainage (PTBD); Gastric cancer; Local recurrence; Chemotherapy

ABBREVIATIONS:
Percutaneous Transhepatic Biliary Drainage (PTBD); Total bilirubin (T-bil); Median Survival Time (MST); Randomized Controlled Trial (RCT); Colony-Stimulating Factor (G-CSF); Quality Of Life (QOL)

ABSTRACT

Background/Aims: We reviewed the medical records of patients with obstructive jaundice caused by the local recurrence of gastric cancer to clarify the role of percutaneous transhepatic biliary drainage (PTBD).

Methodology: Eleven patients with a mean age of 60.1 years (range: 51-71 years) underwent PTBD because of obstructive jaundice caused by the extrahepatic recurrence of gastric cancer.

Results: Jaundice was relieved in all the patients, and the serum total bilirubin (T-bil) level decreased from 12.2 to 2.1mg/dL. No major complications associated with the execution of PTBD occurred. Although various symptoms caused by jaundice, such as anorexia, itching, nausea, abdominal pain, and fever, were relieved in all the patients within one week after PTBD, general fatigue persisted in 3 patients and abdominal fullness persisted in one. Seven of the 11 patients were discharged from the hospital after the execution of PTBD and remained at home for a median of 93 days. The median survival time (MST) of the remaining 4 patients who could not be discharged was 48 days. Chemotherapy was added in 5 patients after the execution of PTBD; these patients exhibited a significantly longer MST of 247 days, compared to 62 days among the patients who did not receive chemotherapy (P=0.0176).

Conclusions: PTBD was safely conducted and improved the quality-of-life of patients with obstructive jaundice caused by the local recurrence of gastric cancer. Furthermore, the use of chemotherapy after PTBD might prolong patient survival although RCT (randomized controlled trial) study should be performed to assess the precise effect of chemotherapy after PTBD.

INTRODUCTION

Extrahepatic biliary obstructions resulting in obstructive jaundice can be caused by various kinds of metastatic carcinoma originating from the colon, breast, lung, cervix, melanoma, and stomach (1,2). The incidence of extrahepatic biliary obstruction associated with the local recurrence of gastric cancer has been reported to be 1.4 to 2.3% (3,4). Since impaired hepatic function, characterized by a high serum total bilirubin (T-bil) level, contraindicates active chemotherapy in patients with malignant biliary obstructions, the prognosis of patients is generally poor (5). However, effective biliary drainage may improve the hepatic function of the patient, making it subsequently feasible to add chemotherapy to their treatment regimen and possibly leading to an improved prognosis. Therefore, we reviewed the medical records of patients with obstructive jaundice caused by the local recurrence of gastric cancer to clarify the role of percutaneous transhepatic biliary drainage (PTBD).

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METHODOLOGY

Patient Characteristics

Between October 1998 and March 2004, 873 patients underwent a gastrectomy for the treatment of primary gastric cancer at the Department of Surgery, Osaka National Hospital (Osaka, Japan). Among them, 11 patients (8 men and 3 women; mean age, 60.1 years; age range, 51-71 years) developed extrahepatic biliary obstructions caused by lymph node recurrences along the hepatoduodenal ligament. The clinical characteristics of the patients are shown in **Table 1**. Five patients had previously undergone a distal gastrectomy and six patients had undergone a total gastrectomy.

RESULTS

Ten of the 11 patients had primary gastric cancers located in the lower third of their stomachs. Morphologically, 4 patients had scirrhous-type advanced gastric cancer and 7 patients had ulcerative-type gastric cancer. Histologically, diffuse-type adenocarcino-

ma was observed in 7 patients. The primary tumor had invaded transmurally beyond the serosa in 9 of the 11 patients. Seven patients had stage IV disease according to the TNM classification (6); the N3 nodes were involved in 6 patients, and three patients had peritoneal dissemination. A curative R0 resection was performed in 7 patients. At the onset of jaundice, 6 patients had a performance status (PS) of 1 and 5 patients had a PS of 2, according to the Eastern Cooperative Oncology Group (ECOG) scale. The median interval between the initial gastrectomy and the onset of obstructive jaundice was 359 days (range: 83-874 days). Other than the metastatic lymph nodes along the hepatoduodenal ligament, 8 patients had distant metastatic lesions involving the liver in 6 patients, the peritoneum in 5 patients (without massive ascites), and the bone in one patient.

Safety and Efficacy of PTBD

All the patients underwent PTBD, and their jaundice was effectively relieved: the serum T-bil level decreased from 12.2mg/dL (range: 4.6-21.3mg/dL) to 2.1mg/dL (range: 0.9-4.7mg/dL) mg/dL. No major complications associated with the execution of PTBD occurred. During the follow-up period after the initial PTBD, 8 of the 11 patients developed incidental cholangitis; these patients were conservatively treated with antibiotics, and their conditions improved. Tube obstructions occurred in 3 patients within a week after the insertion of the PTBD tube, requiring that the tube be exchanged. The obstructions were caused by bile sludge in 1 patient and tube dislocations in 2 patients. Transient hemobilia was seen in one patient.

Various symptoms caused by jaundice, such as anorexia, itching, nausea, abdominal pain, and fever, were relieved in all the patients within one week after PTBD. However general fatigue persisted in 3 patients and abdominal fullness persisted in one patient (**Table 2**). Seven out of the 11 patients were discharged from the hospital after the execution of PTBD and remained at home for a median of 93 days (range: 3-285 days).

Chemotherapy after PTBD

After their jaundice had been relieved using PTBD, 5 patients received chemotherapy, consisting of UFT (tegafur/uracil), irinotecan + cisplatin, S1 (tegafur/CDHP/Potassium Oxonate), S1 + paclitaxel, and 5-fluorouracil + methotrexate, respectively, because these patients fulfilled the following criteria: 1) age ≤76 years; 2) ECOG performance status ≤2; 3) normal bone marrow function (white blood cell count ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10g/dL); 4) normal renal function (creatinine concentration <1.5mg/dL); 5) absence of myocardial, hepatic (T-Bil <2.0mg/dL), and neurologic impairment; and 6) verbal and written informed consent before initiation of chemotherapy. When the clinical characteristics of the patients that did and did not receive chemotherapy were compared, the mean

TABLE 1 Clinical Characteristics of 11 Patients with Obstructive Jaundice caused by the Local Recurrence of Gastric Cancer

Case	Age	Sex	Gastrectomy	Location	Morphology	Histology (intestinal /diffuse)	Stage	Curability	Interval (Gastrectomy–Onset of jaundice)(days)	Maximum value of serum T-Bil (mg/dL)	PS	Combined distant metastasis
1	59	f	distal	L	ulcerative	diffuse	IIIA (t3n1)	B	258	15.7	1	H
2	52	f	distal	L	ulcerative	intestinal	IIIA (t2bn2)	B	145	10.0	1	H
3	67	m	total	LMU	scirrhous	diffuse	IV (t3n3)	B	717	8.6	1	
4	51	f	total	U	scirrhous	diffuse	IV (t3n3)	B	874	21.3	2	P bone
5	67	m	distal	LM	ulcerative	diffuse	IIIA (t3n1)	A	624	19.0	2	H,P
6	56	m	total	LM	ulcerative	diffuse	IV (t4n2H1P1)	C	348	10.4	1	H,P
7	71	m	distal	L	ulcerative	intestinal	IV (t3n3P1CY1)	C	221	9.9	0	H,P
8	60	m	total	LMU	ulcerative	diffuse	IV (t3n3P1)	C	184	4.6	1	P
9	55	m	total	LM	scirrhous	intestinal	IV (t3n3)	A	83	9.0	2	
10	69	m	total	LMU	scirrhous	diffuse	II (t2bn1)	A	275	13.4	2	
11	54	m	distal	L	ulcerative	intestinal	IV (t4n3)	C	217	12.3	2	H

m: male, f: female, *LMU*: lower / middle / upper third of the stomach, H: liver metastasis, P: peritoneal dissemination, CY: cytology of peritoneal lavage.

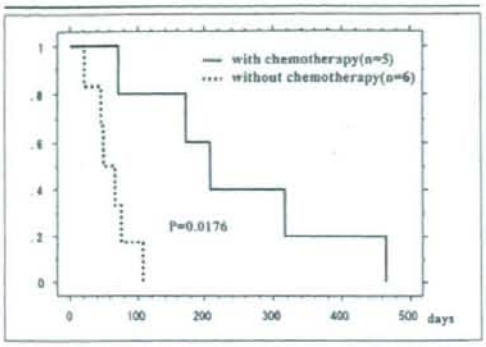

FIGURE 1 Survival after PTBD.

PTBD-induced improvement in the serum T-bil level was significantly lower in the patients who received chemotherapy, as shown in **Table 3** (P=0.03). During the chemotherapy regimens, grade 4 neutropenia was observed in two patients, requiring the administration of granulocyte colony-stimulating factor (G-CSF). Grade 3 diarrhea occurred in one patient, necessitating a dose reduction of S1. Anorexia, rash, and nausea at grades 1 and 2 were commonly observed. The chemotherapy was finally discontinued in all 5 patients because of a deterioration in their PS in 2 patients, an intestinal obstruction caused by peritoneal dissemination in 1 patient, cholangitis in 1 patient, and diarrhea in 1 patient. The median duration of chemotherapy was 201 days (range: 14-360 days).

Survival after PTBD

All the patients eventually died; the median survival time (MST) after the execution of PTBD was 4.9 months (range: 0.7-15.4 months). The five patients who underwent chemotherapy demonstrated a significantly longer MST of 247 days, compared to the remaining 6 patients who had a MST of 62 days (P=0.0176; see **Figure 1**).

DISCUSSION

Metastatic lymphadenopathy along the hepatoduodenal ligament is common as a cause of obstructive jaundice after a gastrectomy for primary gastric cancer (7). Two-thirds of such lymph node metastases causing malignant biliary obstructions were reported to be derived from advanced cancers located in the gastric antrum, close to the hepatoduodenal ligament (7). In this review, the primary gastric cancer had spread in the antrum of the stomach in all but one of the patients, consistent with the findings of the previous report (7). Several other characteristics of the primary tumor demonstrated in this review, such as an ulcerative-type morphology, a diffuse-type histology, and transmural invasion, were also commonly observed in the previous report (7).

In our series, all the patients underwent initial PTBD without experiencing any major complications, such as hemorrhage, shock, or acute pancreatitis. During the follow-up period after PTBD, various complications can occur, including twisting, fracture, obstruction, or dislocation of the inserted tube as well as cholangitis (8-15). Eventually, 8 of the 11 patients developed transient cholangitis, and three patients developed tube obstructions that demanded a tube exchange.

PTBD improved various symptoms caused by obstructive jaundice, as shown in **Table 2**, and improved the patients' quality of life (QOL) though it might be possible to say that PTBD tube itself deteriorated the patients' QOL. General fatigue persisted in 3 of the 11 patients, which is generally considered to be a difficult symptom to eradicate by using only PTBD (16).

Chemotherapy may be contraindicated in patients with malignant biliary obstructions because the chemotherapeutic agents are maintained in the body at a high serum concentration, possibly resulting in a high incidence of adverse effects. Therefore, effective biliary drainage is essential for enabling chemotherapy to be performed safely, thereby improving patient prognosis. In the present series, 5 patients received chemotherapy after the effective relief of their jaundice using PTBD. Grade 4 neutropenia was observed in two patients, and grade 3 diarrhea was observed in one, while any clinical factors such as age, the level of serum T-bil either before or after PTBD, and the duration of jaundice, were not associated with the incidence of adverse effects of chemotherapy. These findings suggest that PTBD does not always guarantee the safety of chemotherapy, even after jaundice has been effectively relieved.

The MST of patients with obstructive jaundice

TABLE 2 Improvement in Symptoms after PTBD

Type of symptom	Number of patients				
	Initial	Disappeared	Improved	Persisted	Deteriorated
Generalized fatigue	8	2	3	3	0
Anorexia	7	0	7	0	0
Skin itching	4	3	1	0	0
Nausea	2	1	1	0	0
Abdominal fullness	2	0	1	1	0
Abdominal pain	1	0	1	0	0
Fever	1	1	0	0	0

TABLE 3 Clinical Characteristics of Patients who Did or Did Not Receive Chemotherapy

	chemo(+) n=5	chemo(-) n=6	*P* value
Male:Female	3:02	5:01	0.546
Mean age (years)	60.8	59.5	0.784
Mean lowest serum T-bil level after PTBD (mg/dL)	0.96	3.03	p=0.029
PS 0 or 1	4	2	0.242
H (+)	3	3	>0.999
P (+)	1	3	0.242

PS: performance status, H: liver metastasis, P: peritoneal metastasis, T-bil: total bilirubin, PTBD: percutaneous transhepatic biliary drainage.

caused by the local recurrence of gastric cancer has been reported to be 2.0-4.2 months, if the patients had received external biliary drainage alone (3,4). On the other hand, chemoradiotherapy (combining external radiation with cisplatin and 5-FU) after PTBD enabled a prolonged survival period of 14.4 months" (17). In our series, the 5 patients who received chemotherapy had a significantly longer MST of 247 days, compared with the other patients who received external drainage alone (**Figure 1**). These findings may suggest a possibility that active treatment in addition to biliary drainage improve the prognosis of patients. However, there seemed to be many other factors affecting these survival differences between the patients with and without chemotherapy. Clinical background imbalance of PS, presence of peritoneal metastasis, or the mean serum T-bil level, as shown in **Table 3**, might be a cause of these differences. In addition, the number of estimated case in our series was too small to obtain a definitive conclusion regarding the significance of additional active treatment after PTBD.

In conclusion, PTBD was conducted safely and improved the QOL of patients with obstructive jaundice caused by the local recurrence of gastric cancer. Furthermore, the use of chemotherapy after PTBD might prolong patient survival although RCT study should be performed to assess the precise effect of chemotherapy after PTBD.

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