Photodynamic Therapy Using Talaporfin Sodium (Laserphyrin®) for Bile Duct Carcinoma: A Preliminary Clinical Trial

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Abstract. *The efficacy of adjuvant photodynamic therapy (PDT) using the new photosensitizer, talaporfin sodium (TPS), was assessed in 7 patients with bile duct carcinoma (BDC). The 664-nm semiconductor laser (100 J/cm^2) was applied through endoscopy to the tumor lesion within 6 h after injection of TPS. Cases included three non-resectable and 4 resected BDC with remnant cancer cells at the bile duct stump. Radiated lesions exhibited mild inflammatory responses. Locally advanced tumor occluding bile duct was relieved by PDT and patency was maintained for 16 months. Two patients developed mild photodermatitis but no severe morbidity. One patient died of other disease, and two patients died of liver metastasis within 6 months, but local recurrence was not observed. Three patients maintained cancer-free survival for 6-13 months. One patient survived with good status for 24 months. Adjuvant TPS-PDT is a safe and useful treatment for local control of BDC. Compared to the conventional PDT, the patient's quality of life is remarkably improved.*

As a result of the improvements in early diagnosis, the number of cases with resectable bile duct carcinoma (BDC) has increased and the patients survival has improved in recent years (1-3). However, curative resection is often difficult because BDC spreads extensively along the bile duct beyond the lesion noted at the pre-operative diagnosis (1). Positive surgical margins at the stump of the hepatic duct are a significantly poor prognostic feature compared to duodenal margin or exposed margin of the bile duct (4). To date, there are no data supporting the survival advantage of adjuvant radiotherapy or chemotherapy after surgery (5, 6). On the other hand, in non-resectable advanced BDC, placement of a metallic stent improves quality of life. However, stent occlusion by tumor in-growth or other causes is frequent, and local ablation therapies have been used for re-canalization (1, 7). To resolve these problems in BDC treatment, effective local treatment is necessary.

Photodynamic therapy (PDT), which is a form of laser treatment, has led to remarkable regression of malignant tumors, including BDC, since the 1980s (8). PDT is based on the use of light to activate photosensitizers and induce cytotoxicity in adjacent tissue. PDT has become a technically feasible and useful modality for the treatment of non-resectable BDC (9-12). In two randomized controlled trials, PDT provided longer survival than bile duct stenting-alone (11, 12). A possible explanation for the improved survival is the powerful anti-tumor immunological responses induced by PDT. Our group has also reported the benefits of PDT using porfimer sodium as chemotherapy for non-resectable BDC or adjuvant chemotherapy after surgery for local control (13). The latest review of PDT for unresectable BDC indicates that in most patients, PDT results in a reduction of serum bilirubin levels, improvement of quality of life, and prolongation of survival time, while having only a few complications (7, 9, 11, 12). Thus, PDT is also apparently a useful modality for local treatment of BDC. The first clinically approved photosensitizer, a hematoporphyrin derivative such as porfimer sodium, was effective for treatment of cholangiocarcinoma (5-12). However, this agent has various clinical drawbacks, such as limitation of permeability of eximer-dye laser in the deep layers and

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prolonged skin photosensitivity. A high tissue penetration and low skin photosensitivity are desirable in the new photosensitizing agents. Mono-L-aspartyl chlorin e6 [NPe6, talaporfin sodium (TPS), Laserphyrin®; Meiji Seika Pharma Co., Ltd., Tokyo, Japan] is a next-generation photosensitizer. The 664-nm of semiconductor laser light (Panasonic Healthcare Co., Ltd., Tokyo, Japan) used for TPS penetrates tissue deeper than does the 630-nm laser light of the eximer dye laser (14-16). Furthermore, TPS-PDT is associated with lower skin phototoxicity compared with photofrin because TPS is degraded rapidly *in vivo* and has excellent anti-tumor activity (15, 17, 18). Our previous reports showed that TPS-PDT was less toxic and more effective in comparison with PDT using porfimer sodium *in vitro* and *in vivo* in an animal model (19, 20). Thus, TPS-PDT is a promising treatment with higher cure rate and less severe side-effects than conventional PDT using porfimer sodium. To our knowledge, there is little or no information on the clinical effect of TPS-PDT in patients with resectable or non-resectable BDC. Based on our basic study and previous reports in lung cancer (14-20), we began a clinical trial of TPS-PDT in patients with BDC, under the permission of the *Institutional Review Board* (*IRB*) at the Nagasaki University Hospital.

Patients and Methods

Patients. The subjects of the study were seven patients with extrahepatic BDC who were admitted to the Division of Surgical Oncology, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between April 2010 and April 2012. The mean age of the patients at the time of surgery was 76.6 years (range 71-85 years), and comprised of six males and a female. Prior to treatments for BDC, patients were treated with endoscopic naso-biliary drainage or percutaneous transhepatic biliary drainage to improve obstructive jaundice but no one received chemo- or radiotherapy. None had any other major disease and all had good performance status before surgery and PDT. Tumors were assessed by computed-tomography, cholangiography, intraductal ultrasonography (20 MHz), brushing cytology or biopsy. The surgical procedures comprised of extended left or right hemihepatectomy with resection of the extrahepatic bile duct, or pancreaticoduodenectomy in four patients. Resections were performed *en bloc* based on the pre-operative imaging diagnosis and lymph node dissection was performed on the hepatoduodenal ligament, surrounding pancreas head and para-aortic lesions. All hepatic tumors were resected without macroscopic exposure of the amputated section; however, microscopic infiltration of cancer cells was diagnosed by pathological examination during and after surgery. Complete resection failed, requiring additional resection of the hepatic duct in all patients. We used the *Classification of Biliary Tract Carcinoma* (21). Our criterion for PDT was BDC without distant metastasis or advanced node metastasis by the imaging or pathological diagnosis. PDT was the first-line local treatment for patients with histological remnant cancer at the amputed bile duct who underwent surgical resection. Additional chemotherapy and radiation therapy would be selected after PDT. The study design was approved by the Ethics Committee of NUGSBS (*IRB permission number 14052347*) on the first of September, 2009 and conflict of interests was not indicated. Signed consent was obtained from each patient before TPS-PDT. As PDT for BDC was not covered by the National Health Care Scheme in Japan, the scientific fund for special research programs at NUGSBS was used for medical expenses associated with PDT for all patients.

PDT protocol. All patients who underwent TPS-PDT were in a stable condition based on physical examination and laboratory tests after surgery or biliary drainage. TPS (NPe6; Laserphyrin® 100 mg for injection; Meiji Seika Pharma., Co. Ltd., Tokyo, Japan) (22), was intravenously injected at a dose of 40 mg/m^2 4-6 hours prior to laser treatment. After injection of TPS, the patient stayed in a dark room (less than 500 lux of light using a black-out curtain) for two weeks to prevent skin phototoxicity (23). Protoporphyrin and uroporphyrin (markers of porphryn metabolites) and conventional blood parameters were monitored before administration of TPS and 1, 3, 5 days after PDT.

Prior to PDT for patients who underwent surgical resection, a 16-18 Fr dilated plastic tube was placed *via* the trans-intestinal route to facilitate endoscopy. In patients with non-resectable BDC 9 Fr preload catheter (ERBD pusher tube; Cook® Inc., Bloomington, IN, USA) (Figure 1a) was firstly placed in the bile duct and the laser fiber was placed near the stenotic lesion *via* a preload catheter. The laser apparatus used was a PDT semiconductor laser (Panasonic Healthcare Co., Ltd., Tokyo, Japan) (Figure 1b) (24). A laser with wavelength of 664 nm±2 nm was applied to two or three target lesions through an endoscope to the anastomotic site of the hepaticojejunostomy or occluded tumor lesion for 10 min (Figure 1a and c). The mean energy supplied was 100 J/cm^2, equivalent to that by PDT using porfimer sodium (23).

Results

Demographics. All seven patients were diagnosed with extrahepatic bile duct carcinomas (Table I). One patient had two skip lesions of bile duct carcinoma and gastric carcinoma of the upper stomach. Three patients had unresectable BDC due to advanced tumor stage and poor general status. Biliary stenting was undertaken before PDT in case 1 and after PDT in cases 2 and 4. Four patients underwent surgical resections and cancer cells were histologically-detected at the stump of the proximal hepatic duct (R1 resection). Three patients underwent hepatectomy combined with resection of the hilar bile duct and two underwent pancreaticoduodenectomy. In cases 3 and 6, cancer had infiltrated to deeper layers of hepatic duct and others showed epithelial extension of the hepatic duct.

PDT treatments. In patients with unresectable BDC, PDT was administered to the stenotic site of BD carcinomas *via* papilla Vater using an endoscopic approach (Table II). Radiation of 100 J/cm^2 was administered to each part. For resected BDC, PDT was administered to the site of the hepaticojejunostomy, in which tumor was not macroscopically observed during surgery. After PDT, biliary stenosis was relieved in case 1. In two patients, acute

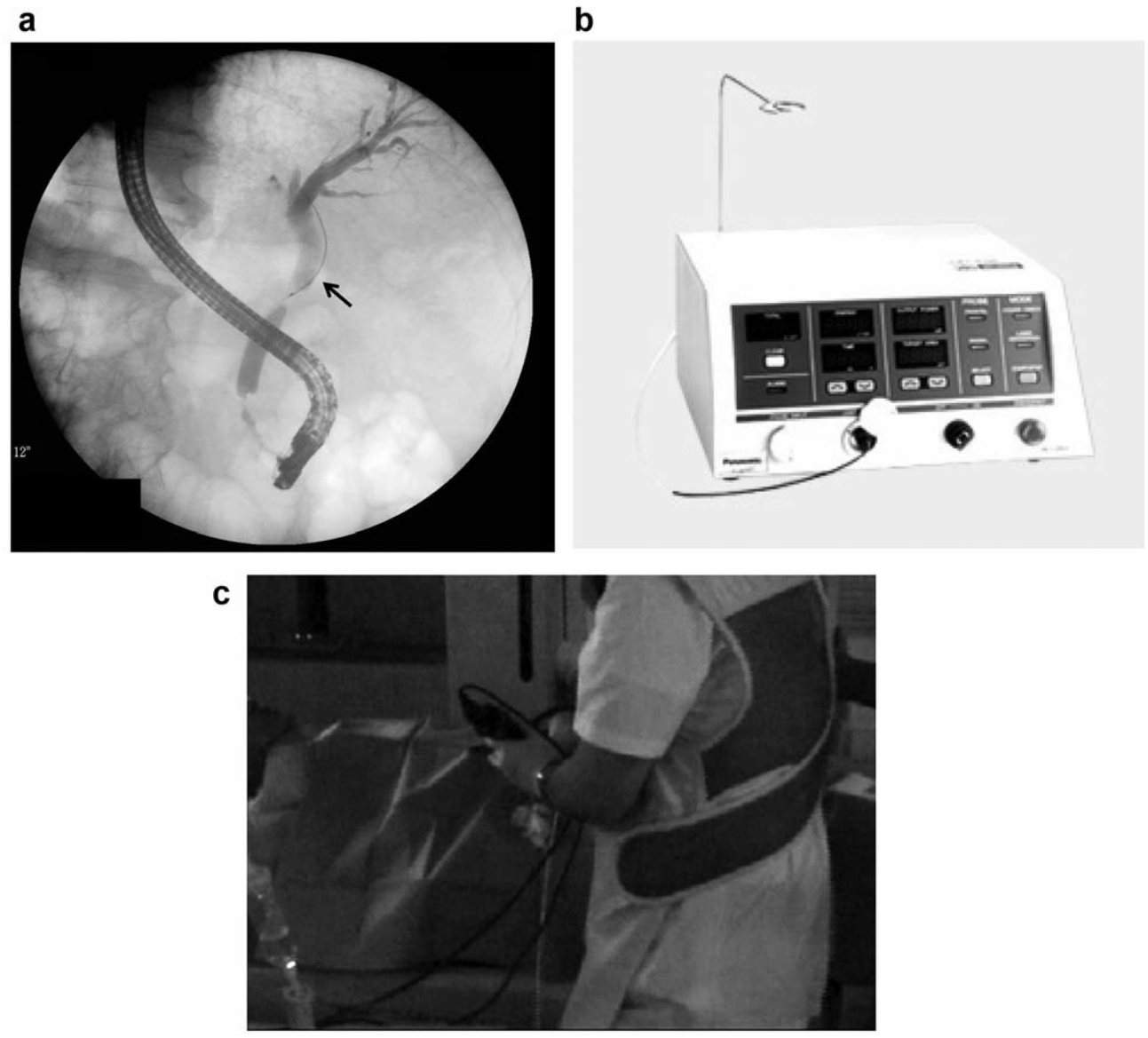

Figure 1. *Talaporfin Sodium-Photodynamic Therapy (TPS-PDT). a):Placement of preload catheter via the papilla Vater using endoscopy and X-ray findings of laser catheter (arrow). The pusher tube was not detected by X-ray this Figure is taken from a Japanese publication (37). b):PDT semiconductor laser (ZH-L5011HJP; Panasonic Healthcare Co., Ltd., Tokyo, Japan. (Figure was reffered from company's web site; http://panasonic.biz/healthcare/pd/). c): Approach for cholangioscopy via an abdominal wall fistula and anastomosed jejunum.*

epithelial or peribiliary inflammation was observed but was transient (Figure 2a and b). All patients were moved to other related hospitals within six days (according to our protocol) and were eventually discharged within 14 days after PDT. In two patients, the irradiated lesion was mildly reddish and edematous immediately after PDT.

Adverse effects. Mild transient cholangitis occurred within a couple of days after PDT in case 7 (Table III). Mild photodermatitis within a couple of days was observed in two patients and one patient had still remarkable skin pigmentation (Figure 3). None of the patients developed serious complications or mortality during hospitalization after PDT. Four patients underwent adjuvant anticancer chemotherapy, such as gemcitabine (Gemzar®; Eli Lilly Co., IN, USA) or S-1 (Taiho Pharma Co. Ltd, Tokyo, Japan). Case 1 did not show tumor progression and biliary occlusion for 16 months, however, he underwent radiation therapy due to tumor progression. Case 1 had the longest survival after PDT in the present series. Two patients died of distant metastasis but had

Table I. *Patients' demographics before photodynamic therapy.*

	Age (years)	Gender	Disease	Operation	Treatments
1	74	M	Widely spreading BDC	No	Probe laparotomy and EMS placement
2	77	M	BDC with gastric carcinoma	No	Endoscopic biliary stenting using plastic tube
3	75	M	Widely spreading BDC	Yes	Rt. HH (Sg5-8, Sg1)+PD
4	78	M	Hilar BDC	No	Endoscopic biliary stenting using plastic tube
5	71	M	Hilar BDC	Yes	Rt. HH (Sg5-8, Sg1)
6	85	F	Hilar BDC	Yes	Lt. HH (Sg2-4, Sg1)
7	77	M	BDC	Yes	SSPPD

BDC; Bile duct carcinoma; EMS: expandable metallic stent; HH: hemihepatectomy; PD: pancreaticoduodenectomy; SSPPD: subtotal stomach-preserving pancreaticoduodenectomy; Sg: Couinaud's segment of the liver, Rt: right, Lt: left.

Table II. *Demographics of patients treated with photodynamic therapy.*

Case	Reason for PDT	Target area for PDT	Light dose	Post-PDT findings
1	Locally advanced stage of BDC	Main BDC	100 J/cm^2, 2 lesions	Relief of biliary stenosis
2	Chronic respiratory failure and gastric cancer	Main BDC	100 J/cm^2, 4 lesions	None
3	Cancer-positive stump of left HD	Anastomotic site of HJ	100 J/cm^2, 3 lesions	None
4	Multiple liver metastasis from BDC	Main BDC	100 J/cm^2, 3 lesions	None
5	Cancer-positive stump of left HD	Anastomotic site of HJ	100 J/cm^2, 3 lesions	Mild inflammation around HD anastomosis
6	Cancer-positive stump of right HD	Anastomotic site of HJ	100 J/cm^2, 4 lesions	None
7	Cancer-positive stump of HD	Anastomotic site of HJ	100 J/cm^2, 3 lesions	Acute inflammation around hepatic hilum

BDC: Bile duct carcinoma; HD: hepatic duct; HJ: hepatico-jejunostomy.

Table III. *Patient outcome after photodynamic therapy.*

Case	Short-term complication	Long-term complications (>1 month)	Adjuvant treatment	Status
1	Mild photodermatitis	Skin pigmentation	Chemotherapy (S-1) RT at 16 months	Alive with cancer (24 months) Cancer progression at 16 months and RT given. Patent of EMS for 20 months
2	Moderately liver dysfunction	None	Chemotherapy (Gem)	Dead due to cardiac infarction (4 months)
3	None	None	Chemotherapy (Gem)	Cancer death by liver metastasis without local recurrence (5 m)
4	No	None	None	Cancer death by liver metastasis (5 months)
5	Mild photodermatitis	None	None	Alive without recurrence (13 months)
6	None	None	Chemotherapy (Gem)	Alive without recurrence (6 months)
7	Mild cholangitis	None	Chemotherapy (S-1)	Alive without recurrence (12 months)

RT: Radiation therapy; EMS: expandable metallic stent; Gem: gemcitabine.

no local tumor progression. One patient died of other causes. Three patients had had no tumor relapse between 6 and 13 months.

Examination of porphyrin levels. Table IV shows the changes in conventional laboratory parameters and the levels of protoporphyrin and uroporphyrin after PDT. The inflammatory parameter of C-reactive protein was significantly increased at day one but not severely high, and had mostly improved at five days. Increase of hepato-biliary enzymes at day one was not remarkable. The protoporphyrin and uroporphyrin levels within five days were not remarkably changed even in the two patients who had photodermatitis.

Discussion

Except for surgically-curative resection, novel treatments as chemotherapy or radiation therapy have not shown any

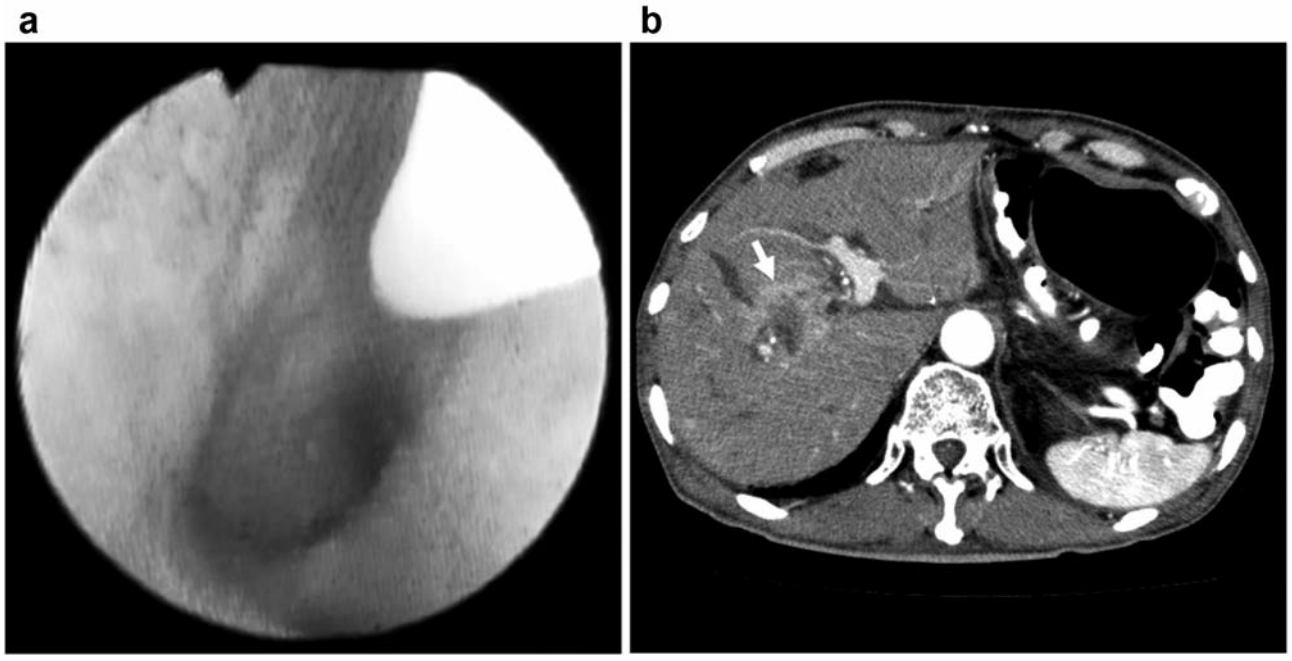

Figure 2. *a):Cholangioscopic findings of the bile duct at the hepaticojejunostomy. Mucosal degeneration with acute mild inflammation as redness or edematous changes were observed during laser radiation. b):Acute inflammatory response represented by a high density area at the periductal lesions by computed-tomography. These Figures are taken from a Japanese publication (37).*

Table IV. *Changes in laboratory data after photodynamic therapy (PDT).*

	Pre-PDT	Day 1	Day 5
White blood cells (/mm^3)	4400±1340	4788±2345	4220±1205
C-reactive protein (mg/dl)	1.03±0.76	3.22±2.45*	1.55±0.97
Hemoglobin (g/dl)	10.2±1.88	10.1±0.99	9.89±1.12
Total bilirubin (mg/dl)	2.51±2.58	3.10±1.74	2.88±1.56
Alanine-aminotransferase (IU/l)	45±56	106±118	88±74
Alkaline phosphatase (IU/l)	623±554	859±618	833±778
Amylase (IU/l)	58±26	76±32	66±29
Creatinine (mg/dl)	0.7±0.1	0.7±0.2	0.6±0.1
Protoporphyrin (μg/dl)	62±14	58±21	56±19
Uroporphyrin (μg/dl)	38±19	45±18	44±14

Data are mean±SD. *p<0.05 *vs*. pre-PDT.

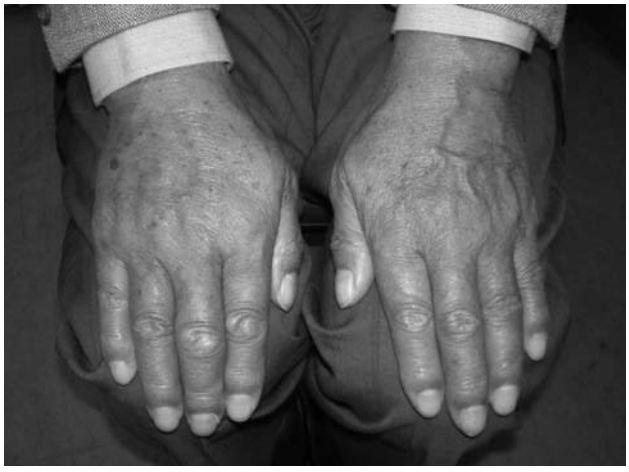

Figure 3. *Photosensitive dermatitis on the exposed skin at two months after. These figures are taken from a Japanese publication (37).*

evidence of efficacy as local treatments for tumor progression. Tamada and Sugano found that results of the use of only metallic stents for non-resectable BDC were disappointing because of the high rate of occlusion by tumor growth, and therefore, PDT presumably also leads to improved patient quality of life and increased survival in such patients (1). As described by some reports including randomized controlled trials, PDT provided better performance status, improvement of obstructive jaundice and a longer survival, and, recently, PDT has been widely applied for BDT treatments in Europe, USA and in eastern Asia (8-12, 25-27). Therefore, PDT is a promising treatment modality to augment conventional anticancer chemotherapy and brachytherapy (5, 28). Despite of efficacy of tumor necrosis by PDT, the long period of skin photosensitivity has

been an obstacle to a more widespread use of PDT (15, 17-19). In Japan, maintenance of pulse laser apparatuses using eximer dye laser for porfimer sodium has been discontinued and, therefore, new and effective photosensitizer and accompanying laser apparatuses, such as a TPS which have been already used for treating bronchial cancer (14-16), have to be applied. In addition, the 664-nm semiconductor laser light was found to have better efficacy in comparison with eximer dye laser (29). To our knowledge, application of PDT using TPS in patients with BDC has not been reported before.

Pahernik *et al*. reported that the benefit of PDT is specific to cancer tissues compared to normal surrounding tissue by difference in accumulation of the photosensitizer between normal and cancer cells (30). TPS-PDT also exhibits a highly tumor-specific effect of tumor necrosis similar to that for PDT using porfimer sodium. In the present study, normal epithelium was also mildly de-generated but this change was not critical and was transient after PDT. Although the total light dose ranged between 200 and 400 J/cm^2, acute inflammatory responses and liver dysfunction were limited, within five days. Furthermore, the neighboring liver parenchyma exhibited an extensive response with findings of acute inflammation by TPS-PDT in Case 7. Laser deeply penetrating surrounding tissues is somewhat of a concern as liver damage and, on the other hand, cytocidal effect for deep lesions of BDC by PDT would be expected. In cases of PDT using porfimer sodium, complete necrosis of cancer cells was limited to up to 4 mm from the epithelial surface of the bile duct (31). We expect a greater penetrating effect of TPS-PDT due to the longer wavelength of the semiconductor laser (664 nm) in comparison with the eximer pulse laser (630 nm) (24). By comparing the high energy of a laser beam such as a YAG laser or of microwave coagulation, the energy level of laser used for PDT of the irradiated lesion is lower and, therefore, safety for normal tissues can be maintained (1, 5, 11, 12, 25). With respect to drug toxicity, TPS-PDT in the present series might be safer in comparison with the conventional PDT using porfimer sodium. Rumalla *et al*. also reported skin phototoxicity after PDT in a few patients (32); this is a major concern during follow-up after PDT. In particular, photodermatitis over two weeks was observed only in the first case (14%). Our previous study using PDT with porfimer sodium found that 8 out of 14 patients (57%) exhibited prolonged skin tanning for one month by photodermatitis. Other studies also revealed lower photosensitivity of TPS in comparison with porfimer sodium (15, 17-20). In the present study, we also examined metabolites of photosensitizer by measuring the concentration of protoporphyrin and uroporphyrin in patients, however, these concentrations were not increased in our series, although these levels progressively increased at four weeks after PDT using porfimer sodium (13). Therefore, by comparing previous experience, the lower residual amount of TPS (possibly early metabolism) might have resulted in a lower rate of photodermatitis in the present study. We believe that the present findings clarify the safety of TPS-PDT.

Wiedmann *et al*. were the first group that succeeded in applying PDT to resectable BDC as an adjuvant therapy for positive surgical margins after resection (31). In cases in which BDC spreads widely along the bile duct, complete resection (R0 resection) is often difficult (3, 4). Matull *et al*. reported that prognosis in patients with biliary tract carcinoma with R1 or 2 resection (in cases of cancer remnant) was similar to that for patients with non-resectable biliary carcinoma who underwent PDT and, therefore, local control by PDT seemed to be effective (33). In our series, non-curative surgery due to positive bile duct stump notably influenced patient survival (34). Our previous findings regarding efficacy of PDT using porfimer sodium showed the significantly longer cancer-free survival (15 months) in comparison with that of patients not treated with PDT (8 months) (13). In the present study, three patients maintained cancer-free survival for a short period of up to 13 months. We still need a larger number of patients and a longer follow-up period for firm conclusions to be drawn. Our experimental study showed that the cytocidal effect of TPS-PDT was significantly increased in comparison with that of PDT using porfimer sodium in a mouse model (20) and, therefore, we expected greater efficacy of tumor necrosis or apoptosis by TPS-PDT. On the other hand in the present study, two patients died in the early period after PDT and distant metastasis was the cause of death, which was similar to our previous experience with conventional PDT (13). The usefulness of PDT combined with other anticancer drugs has been reported (35). Our recent experimental study showed the synergic effect of PDT combined with novel anticancer drugs (unpublished data). By applying adjuvant PDT combined with other chemotherapy, occurrence of distant metastasis may be prevented. In the two patients with distant metastasis, chemotherapy could not be performed due to poor recovery after surgery. Neoadjuvant chemotherapy before surgery may solve the problem of poor compliance with anticancer drug therapy (36). One patient with a locally-progressive BDC had a longer survival after TPS-PDT with biliary stent and combined chemotherapy. Tumor in-growth after placement of the biliary stent did not occur for a long time and this survival is the longest in patients with non-resectable BDC who underwent PDT at our institute, although the patient underwent radiation therapy at 16 months. Previous studies also showed the longer patency of biliary stent by PDT compared with that in patients without PDT, including our experiences (9-13). Thus, multidisciplinary therapy mainly including PDT for patients

with BDC would provide improved survival. In comparison with chemotherapy and radiotherapy, the period of treatment and side effects of PDT is likely to be more convenient.

In conclusion, a next-generation new photodynamic therapy, TPS-PDT, was performed on seven patients with BDC who had remnant tumor cells at the stump of the hepatic duct after surgical resection or who had non-resectable cancer. TPS-PDT might be safer in comparison with PDT using porfimer sodium, and was effective for the local control of tumor growth for a prolonged period. Adjuvant TPS-PDT therapy is therefore apparently a safe and useful option for improved survival in patients with resectable and non-resectable BDC, and represents an important area for future clinical randomized trials.

Conflicts of Interest

We hereby state that we have no conflict of interests regarding the present manuscript and clinical study.

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Figure 1a, 2a, 2b and 3 were taken from a Japanese publication (37), which were permitted by the editorial board of Japan Biliary Association. Figure 1b was taken from web site of Panasonic Healthcare Co., Ltd., Tokyo, Japan.

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