

Selection of biliary drainage route and the effect of adjunctive therapy for unresectable malignant biliary stricture

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ABSTRACT

The outcome of combination of biliary tract drainage with other adjunctive therapies for unresectable malignant biliary tract stricture was evaluated in the 135 patients with known outcome treated in this unit between June, 1986 and May, 1998.

Compared to percutaneous transhepatic drainage, transpapillary drainage significantly shortened the jaundice reduction period but yielded a slightly inferior technical success rate. The efficacy of transpapillary drainage for jaundice was extremely poor in cases of stricture in the upper part of the biliary tract.

A histological comparison of bile duct lumen after various adjunctive therapies showed that intraluminal therapy was much more effective than extracorporeal radiation. Adjunctive therapies significantly increased the survival period in patients with cholangiocarcinoma but they were less effective in patients with pancreatic carcinoma and not effective at all in patients with gallbladder carcinoma. Intraluminal therapy markedly prolonged the internal fistula maintenance period and was effective in improving the quality of life in patients with superior bile duct stricture at multiple sites. The hospital stay was significantly longer in patients who received adjunctive therapy than in those who received biliary tract drainage alone. This finding suggests that adjunctive therapy should not be conducted if it is not expected to result in an increase in the survival period that compensates for disadvantages of a prolonged hospital stay.

In conclusion, in the treatment of inoperable malignant biliary tract stricture, adjunctive therapy should be conducted whenever possible in combination with percutaneous biliary tract drainage, which enable intraluminal therapy, in patients with cholangiocarcinoma. However, biliary tract drainage alone is recommended in patients with pancreatic and gallbladder carcinoma because adjunctive therapy does not seem to be effective. A transpapillary approach is recommended for pancreatic carcinoma, while a percutaneous or transpapillary approach should be selected as appropriate depending on the site of stricture in patients with gallbladder carcinoma.

INTRODUCTION

With the development of sophisticated diagnostic imaging and the refinement of operative

techniques in recent years, results of surgical treatment for malignant biliary strictures have been gradually improving^{1, 2)}, but lesions are still frequently diagnosed as unresectable.

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While percutaneous transhepatic procedures for relief of jaundice³⁾ have been extensively used in cases of malignant biliary strictures causing obstructive jaundice, endoscopic techniques to relieve jaundice⁴⁾ have also become widely undertaken.

Relatively gratifying therapeutic results with those procedures have been reported^{3, 4)}, yet no unanimous conclusion has been reached as to individual indications. Furthermore, it is true that such procedures for relief of jaundice afford no therapeutic effect on primary diseases producing biliary strictures whilst they do provide a definite benefit of improving cholestasis caused about by biliary stricture.

We have striven to improve the prognosis by various jaundice-relieving procedures combined with adjunctive therapy in cases of unresectable malignant biliary strictures. This report deals with the points at issue the proper selection of biliary drainage route for unresectable malignant biliary stricture, based on the results of treatment we have obtained.

SUBJECTS

The subjects studied were 135 patients of malignant biliary stricture with known outcome encountered in this department from June, 1986 to May, 1998. They included 65 cases of cholangiocarcinoma, 54 cases of carcinoma of the pancreas and 16 cases of carcinoma of the gallbladder. The patients ranged in age from 34 to 93 years (mean: 70.3 years), with a male-to-female ratio of 70:65. Clinical stages of the disease were Stage II in 4 cases, Stage III in 28 cases and Stage IV in 33 of the 65 cases of cholangiocarcinoma; Stage III in 12 cases and Stage IV in 42 of the 54 cases of carcinoma of the pancreas; and Stage IV in all the 16 cases of carcinoma of the gallbladder. Malignancy of the disorders was diagnostically established based on biopsy or bile juice cytological findings in all cases except those in which malignant infiltration of contiguous strictures was evident on imaging diagnosis. The staging of diseases was performed based on imaging diagnosed in accordance with the General Rules for Surgical and Pathological Studies of Cancer of the Biliary Tract in Japan⁵⁾ and General Rules for Surgical and Pathological Studies of Cancer of the Pancreas in Japan⁶⁾.

METHODS

1. Biliary drainage

For biliary drainage, the transpapillary approach and the percutaneous transhepatic approach were adopted. Biliary drainage with the transpapillary approach (endoscopic biliary drainage: EBD) consisted primarily of relieving jaundice by endoscopic naso-biliary drainage (ENBD) with 5–6 Fr catheters and subsequent duodenoscopic stenting at the site of stricture with 10–12 Fr stents for internal drainage. Biliary drainage with the percutaneous transhepatic approach (Percutaneous transhepatic biliary drainage: PTBD) consisted of relief of jaundice via catheterization with an 11 Fr catheter and subsequent stenting at the site of stricture with 14–16 Fr stent for internal drainage.

2. Adjunctive Therapy

Adjunctive therapy for the primary disease producing biliary stricture included external radiotherapy (ERT) and cholangial intraluminal therapy. The latter comprised intraluminal radiotherapy (IRT) and/or cholangioscopic therapy, the choice depended on the case.

1) External radiotherapy (ERT)

ERT consisted of antero-posterior two-field opposing supervoltage irradiation with a linear accelerator, as a rule. Each irradiation dose was 2.0 Gy, and the total dose was 50–60 Gy in case of ERT alone or 20–30 Gy if combined with cholangial intraluminal therapy.

2) Cholangial intraluminal therapy

i) Intraluminal radiotherapy (IRT)

IRT was performed with a remote controlled after-loading system (RALS) using ⁶⁰Co as the source. With a source center-object distance of 10 mm a course of 30 Gy IRT was carried out in 6 Gy doses given once a week, or a course of 32 Gy was given in 4 Gy doses twice a week.

ii) Cholangioscopic therapy

In all pertinent cases, cholangioscopic therapy was conducted by means of Percutaneous transhepatic cholangioscope (PTCS), with an adjunctive technique of ① high-power laser therapy or ② photodynamic therapy.

① High-power laser therapy

High-power laser therapy with an Nd-YAG laser was undertaken to relieve stenosis or to reduce tumor bulk. The Nd-YAG laser irradiation was carried out at 15–20 W for 0.5–1.0

second with a contact type probe, or at 30–40 W for 0.5–1.0 second with a non-contact type probe.

② Photodynamic therapy

In the cases with relative small tumor bulk, photodynamic therapy was performed. An eximer dye laser beam was delivered approximately 48 hours after a 2 mg/kg intravenous dose of porfimer sodium as a photosensitizer. The eximer dye laser irradiation was carried out in a dose of 500 mJ/cm² as in PDT for lung cancer with a cylindrical laser probe.

ASSESSMENTS

1. Therapeutic Results of Biliary Drainage

Results of the biliary drainage were evaluated by comparative assessment of procedural success rate, jaundice-relieving effect and duration to jaundice relief according to the approach route, i.e. EBD or PTBD. The assessment of the jaundice-relieving effect and duration to jaundice relief were made in 114 patients whose predrainage serum total bilirubin values were 5.0 mg/dl or more, while 21 patients with predrainage serum total bilirubin values of less than 5.0 mg/dl or whose biliary tract had been prophylactically stented prior to onset of jaundice were excluded.

The biliary drainage was considered to be effective in relieving jaundice if a decrease in serum total bilirubin to less than 5.0 mg/dl occurred following the procedure. The duration to jaundice relief was defined as the number of days required till a fall of serum total bilirubin to below 5.0 mg/dl after drainage.

2. Local Tumor Control Effect of Adjunctive Therapy evaluated by Cholangioscopic Biopsy Findings.

Cholangioscopic biopsy was performed following completion of adjunctive therapy and the local tumor control effect of the adjunctive therapy was evaluated. Of 47 patients who received adjunctive therapy besides biliary drainage, there were 35 patients who were eligible for histologic evaluation of the effects of adjunctive therapy based on cholangioscopic biopsies performed before the start and after the completion of the adjunctive therapy. The local tumor control effect in terms of biopsy histologic findings was assessed in these patients classified according to the type of adjunctive therapy: ERT alone group (n = 8),

Cholangial intraluminal therapy alone group (n = 13), and combined cholangial intraluminal therapy-ERT group (n = 14).

3. Survival-Improving Effect of Adjunctive Therapy

Survival-improving effect of adjunctive therapy was assessed in terms of the cumulative survival rate based on the survival time which was counted from the day of biliary drainage, with patients receiving biliary drainage alone taken as controls. Firstly, all patients were assessed as to cumulative survival rate, and then were assessed by clinical entity and by presence or absence of adjunctive therapy. Furthermore, patients not receiving adjunctive therapy were also assessed for cumulative survival rate by type of disease, and the survival period was compared with cases of unresected tumors classified by type of disease.

Since the clinical picture varies greatly according to the location of the stricture lesion in cholangiocarcinoma, survival rate data were analyzed in patients classified by site of biliary stricture (upper bile duct or lower bile duct) and by the presence or absence of adjunctive therapy. The term of upper bile duct here refers to the superior bile duct (Bs) and the portal bile duct (Bp), and the term of lower bile duct refers to the inferior bile duct (Bi) and the middle bile duct (Bm), according to the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract in Japan⁵⁾.

In view of the diversity of adjunctive therapy undertaken in the cases of cholangiocarcinoma, the survival rate were assessed by classifying the cases into four groups according to type of adjunctive therapy (group 1, no adjunctive therapy; group 2, ERT alone; group 3, cholangial intraluminal therapy alone; group 4, combined ERT-cholangial intraluminal therapy).

4. Internal Biliary Drainage Duration and Adjunctive Therapy.

To evaluate the clinical usefulness of cholangial intraluminal therapy, 44 patients with upper bile duct stricture, which has been reported⁷⁾ to be more frequently complicated by cholangitis after internal biliary drainage, were assessed as to internal drainage duration and its proportion to survival time upon

Table 1 Results of biliary drainage according to approach

	Transpapillary approach (EBD) (n = 40)	Transhepatic approach (PTBD) (n = 74)
Serum bilirubin level before biliary drainage (mg/dl)	14.7 ± 7.2	15.6 ± 7.0
Efficacy of biliary drainage (%)	79.3	92.9
Duration to relief of jaundice (days)	11.3 ± 10.8	17.8 ± 12.2

*p < 0.05

classification by the presence of adjunctive therapy.

5. Hospitalization Period and Adjunctive Therapy

The duration of hospital stay was compared between patients receiving biliary drainage alone and those receiving biliary drainage plus adjunctive therapy, to evaluate the effect of adjunctive therapy on treatment duration. Of cases of cholangiocarcinoma, the comparison was made also by further classifying the patients according to site of stricture (upper bile duct and lower bile duct), and by type of adjunctive therapy.

6. Statistical Analysis

The data of therapeutic effects of biliary drainage were analyzed by means of the unpaired student's t-test. Analysis of internal biliary drainage duration and duration of hospitalization were performed using Mann-Whitney U-test and Kruskal-Wallis test. The cumulative survival rate was calculated with the Kaplan-Meier procedure and assessed using the log-rank test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

1. Therapeutic Effects of Biliary Drainage

1) Procedural success rate and frequency of complications by approach route

EBD was tried on 52 of the 135 study subjects, and was successful in 40 of those patients, hence the success rate was 76.9%. We performed PTBD for 12 patients whom failed for EBD. PTBD was successful in all 95 patients

in whom this procedure was performed, thus the success rate was 100%.

Of the patients undergoing EBD, complications were encountered in 3 patients, including hemorrhage in 1 case (2.5%) and cholangitis in 3 cases (7.5%). The complications associated with PTBD included biliary tract bleeding in 8 cases (8.4%), cholangitis in 5 cases (5.3%), dislodged drainage tube in 5 cases (5.3%), and pneumothorax in 3 cases (3.2%).

2) Serum total bilirubin prior to relief of jaundice, jaundice-relieving efficacy rate and duration to relief of jaundice (Table 1)

There was no significant difference between the EBD group and the PTBD group with respect to serum total bilirubin concentration prior to biliary drainage, nor any significant intergroup difference in jaundice-relieving efficacy rate. The mean duration for decreasing of serum total bilirubin to below 5mg/dl was significantly shorter for the EBD group (11.3 ± 10.8 days) than for the PTBD group (17.8 ± 12.2 days) ($p < 0.05$).

3) Therapeutic outcome of EBD and PTBD in relation to location of stricture (Table 2)

Strictures were located in the upper biliary tract in 60 cases and in the lower biliary tract in 54 cases. In the EBD group, there were a few cases in which an effective relief of jaundice from upper biliary tract stricture was attained. In patients with lower biliary tract stricture, the duration to relief of jaundice was prone to be longer for the PTBD group than with the EBD group.

Table 2 Results of biliary drainage in relation to biliary tract stricture locating and approach route

	Upper stricture (n = 60)		Lower stricture (n = 54)	
	EBD (n = 8)	PTBD (n = 52)	EBD (n = 32)	PTBD (n = 22)
Serum bilirubin level before biliary drainage (mg/dl)	20.3 ± 8.3	15.9 ± 7.5	13.7 ± 6.8	15.4 ± 6.5
Efficacy of biliary drainage (%)	28.6	87.2	95.5	100
Duration to relief of jaundice (days)	15.2 ± 8.3	19.4 ± 12.0	11.3 ± 10.8	16.2 ± 11.9

*p < 0.01 EBD : Endoscopic Biliary Drainage.
PTBD : Percutaneous Transhepatic Biliary Drainage

2. Local Tumor Control Effect of Adjunctive Therapy evaluated by Cholangioscopic Biopsy Findings

There were 8 patients who received ERT alone, only 25.0% (2/8) had biopsy findings negative for cancer. 13 patients received cholangial intraluminal therapy, 69.2% (9/13) had biopsy findings negative for cancer. There were 14 patients who received a combination of cholangial intraluminal therapy and ERT, 78.6% (11/14) had biopsy findings negative for cancer.

3. Survival-Improving Effect of Adjunctive Therapy

1) Survival time in cases of unresected malignant biliary strictures

Comparison of cumulative survival rate and mean survival rate made between the group of all cases receiving biliary drainage alone and the group of those receiving biliary drainage plus adjunctive therapy, disclosed a significant prolongation of survival time for the latter group ($p < 0.05$, Fig. 1-a). When the data were further assessed by classification according to clinical entity, the mean survival time was found to be significantly prolonged for cases receiving adjunctive therapy in cholangiocarcinoma ($p < 0.05$, Fig. 1-b). In carcinoma of the pancreas, the mean survival time tended to be prolonged, though with no statistical significance, for cases receiving adjunctive therapy (Fig. 1-c). In carcinoma of the gallbladder, there was little or no improvement of mean survival time, despite adjunctive therapy (Fig. 1-d). No significant difference in cumulative survival rate among the clinical entities when

cases receiving biliary drainage alone were compared (Fig. 1-e).

2) Survival time in cases of unresected cholangiocarcinoma

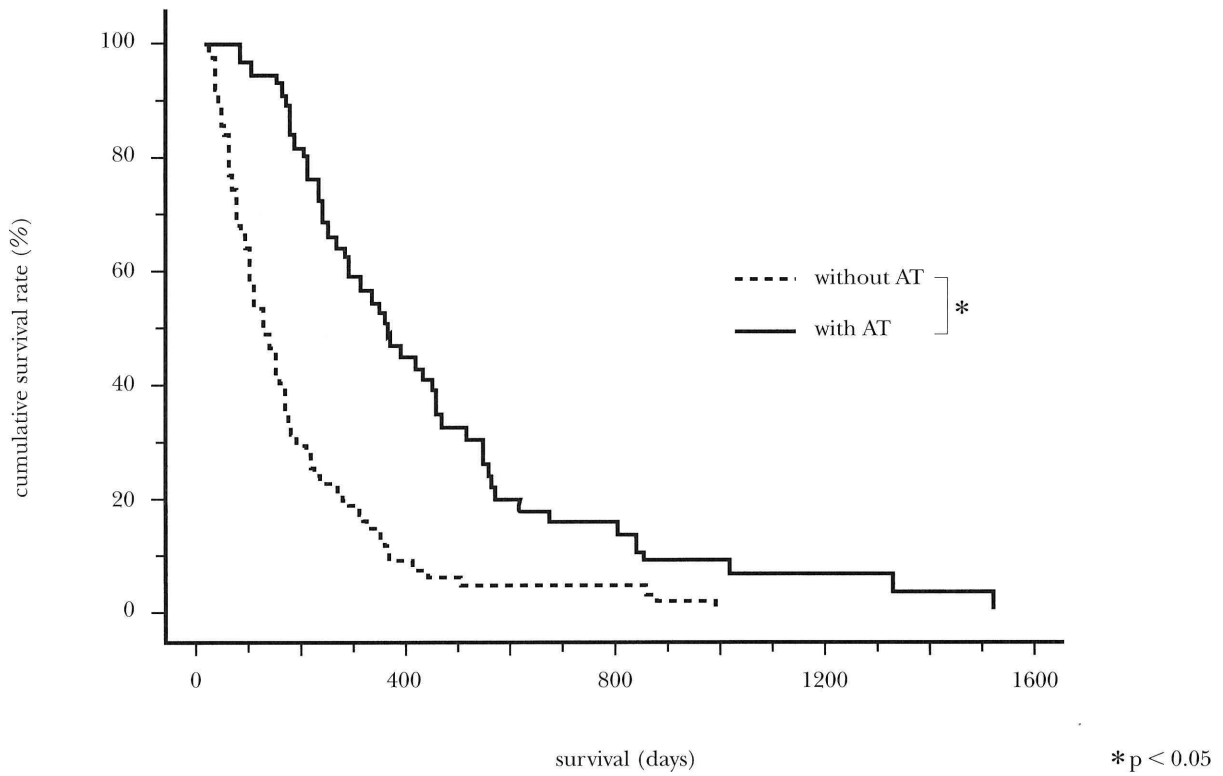
i) Survival time by location of stricture
In lower biliary stricture, the survival time was significantly prolonged for the group receiving adjunctive therapy, compared with the group receiving biliary drainage alone ($p < 0.05$, Fig. 2-a). There was a significant prolongation of survival time for the group with upper biliary strictures receiving adjunctive therapy ($p < 0.01$, Fig. 2-b).

ii) Survival time according to type of adjunctive therapy

As compared with group 1 receiving biliary drainage alone, the survival rate was significantly improved in groups 2 and 4 ($p < 0.01$) while group 3 showed no such improvement. There was no significant difference between group 2 and 4 (Fig. 2-c).

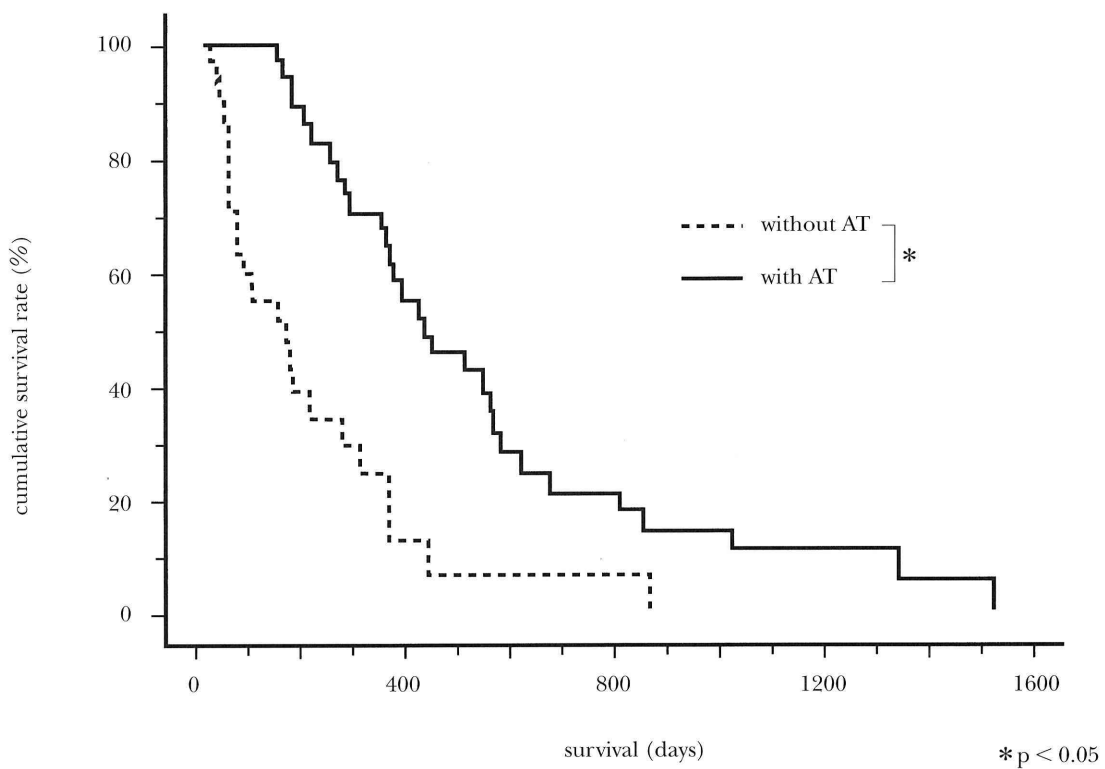
4. Internal Biliary Drainage Duration

Of 44 patients with portal-upper cholangiocarcinoma, 27 patients underwent internal biliary drainage and received adjunctive therapy. Of these, 12 patients received ERT alone (ERT group) and 11 patients received a combination of cholangial intraluminal therapy and ERT (combination treatment group). The mean survival time did not significantly differ between the single treatment group (636.6 ± 417.5 days) and the combination treatment group (621.3 ± 443.9 days). Nevertheless, the duration for which the constructed internal biliary drainage was maintained intact was significantly longer for the combination treat-



*p < 0.05

Fig. 1-a Cumulative survival rates of malignant biliary stenosis cases treated with or without adjunctive therapy. There was a significant difference between the two groups ($p < 0.05$). AT: adjunctive therapy



*p < 0.05

Fig. 1-b Cumulative survival rates of cholangiocarcinoma cases treated with or without adjunctive therapy. There was a significant difference between the two groups ($p < 0.05$). AT: adjunctive therapy

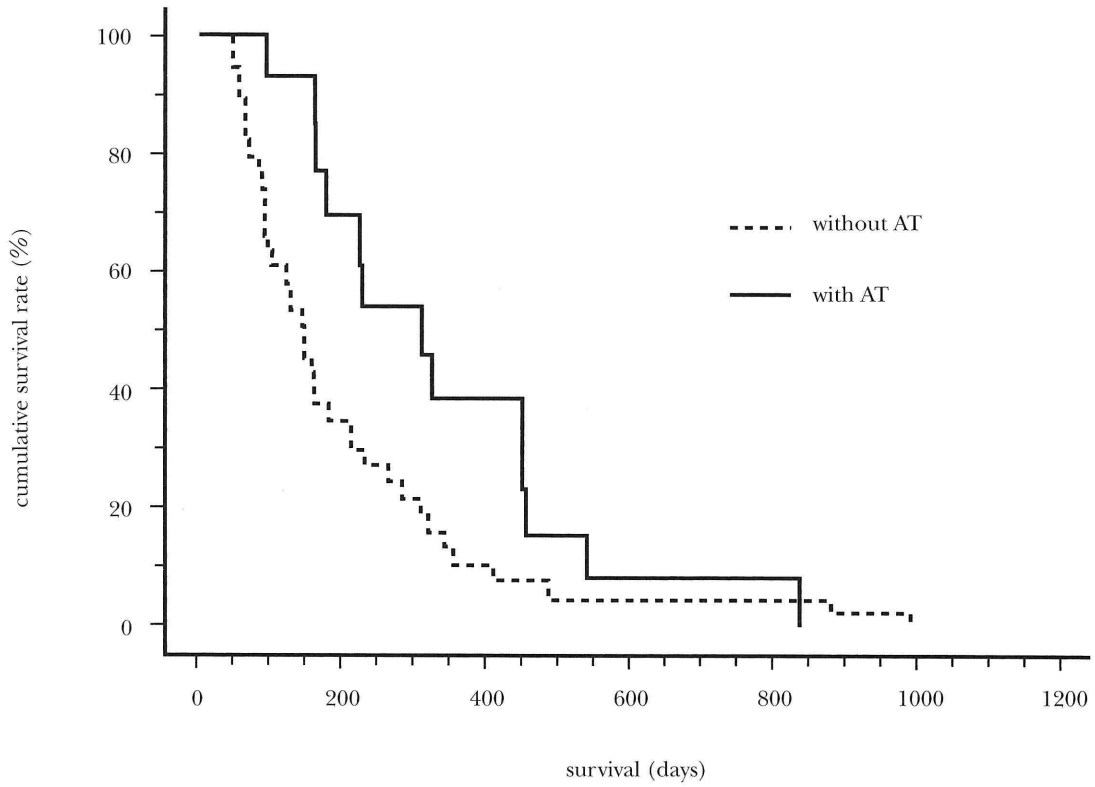


Fig. 1-c Cumulative survival rates of pancreas carcinoma cases treated with or without adjunctive therapy. No significant difference was demonstrated. AT: adjunctive therapy

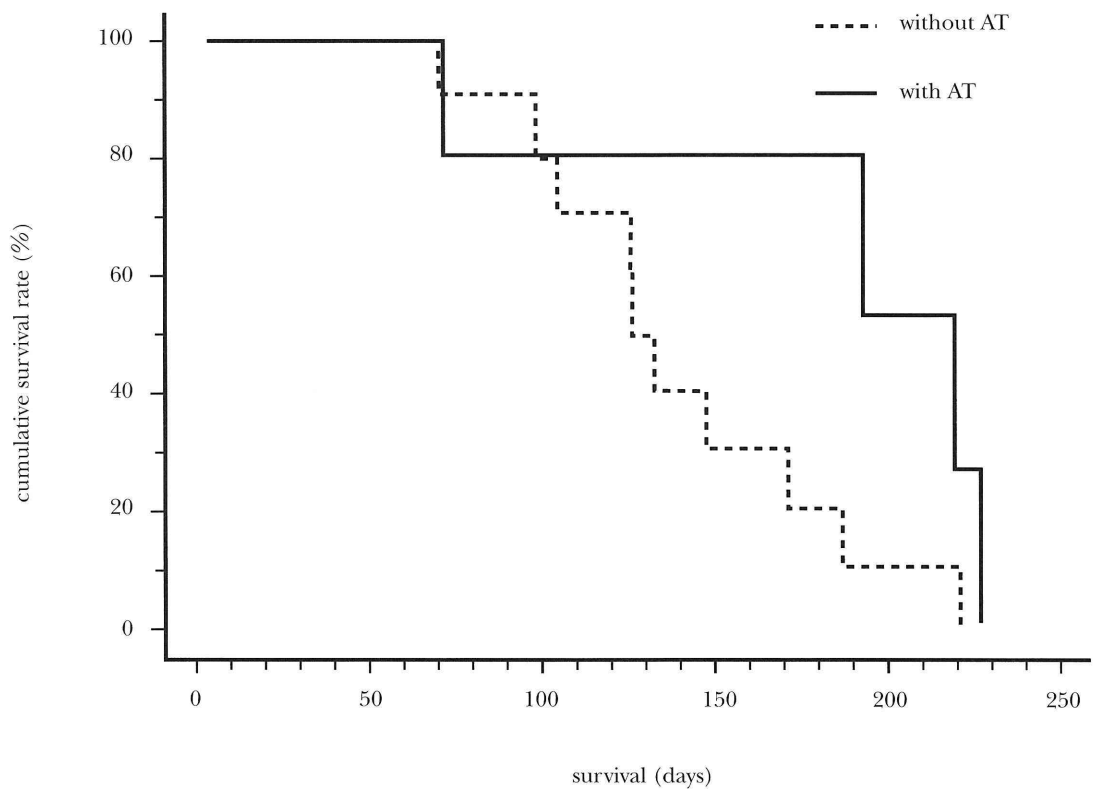


Fig. 1-d Cumulative survival rates of gallbladder carcinoma cases treated with or without adjunctive therapy. No significant difference was demonstrated. AT: adjunctive therapy

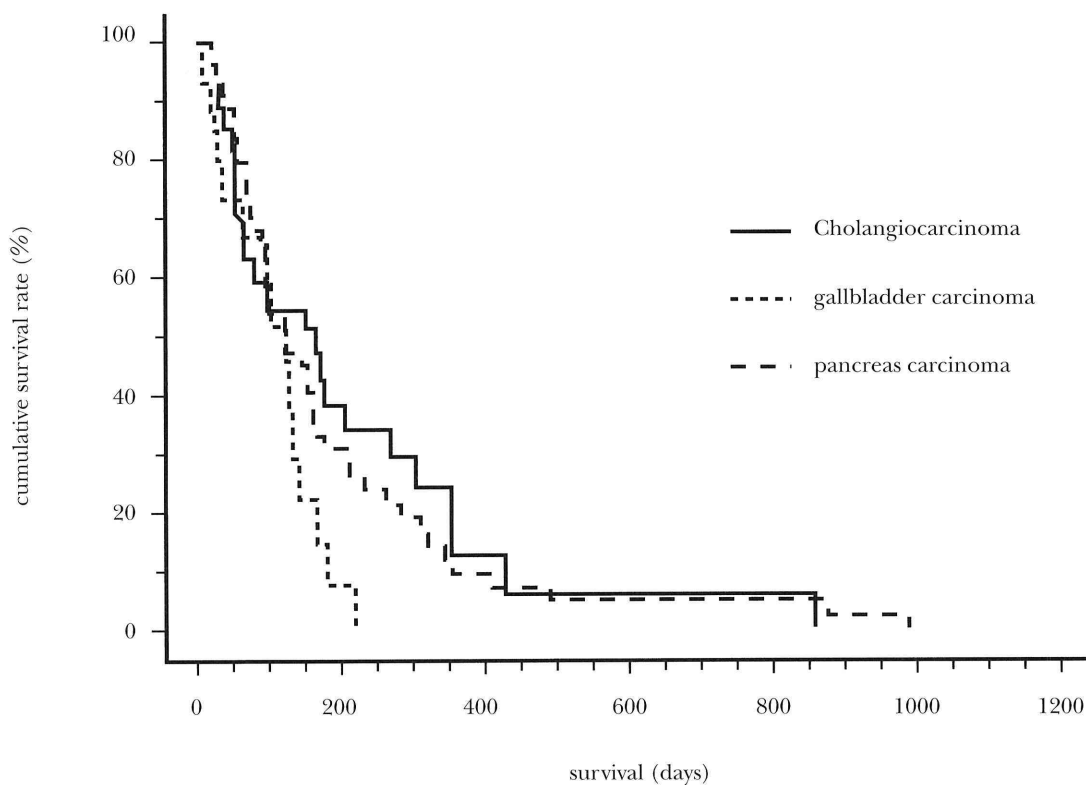


Fig. 1-e Cumulative survival rates of malignant biliary stenosis cases without adjunctive therapy. No significant difference was demonstrated among cholangiocarcinoma, gallbladder carcinoma and pancreas carcinoma.

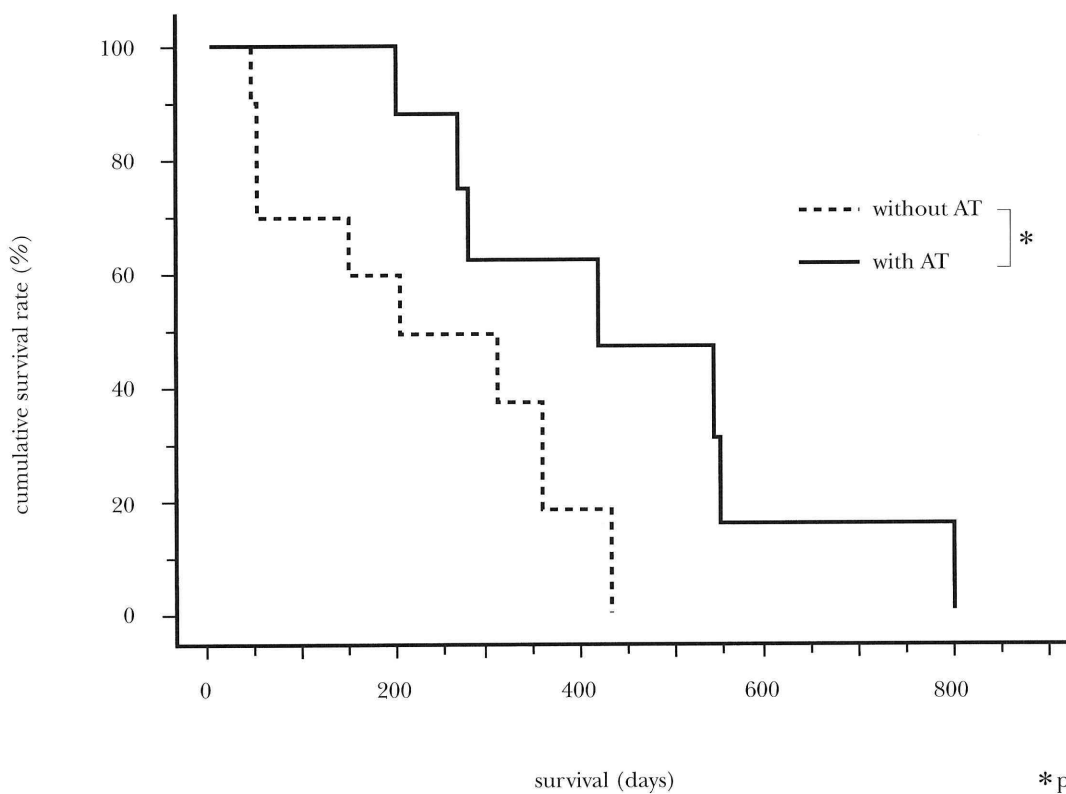


Fig. 2-a Cumulative survival rates of cholangiocarcinoma cases (lower biliary stricture) treated with or without adjunctive therapy. There was a significant difference between the two groups ($p < 0.05$). AT: adjunctive therapy

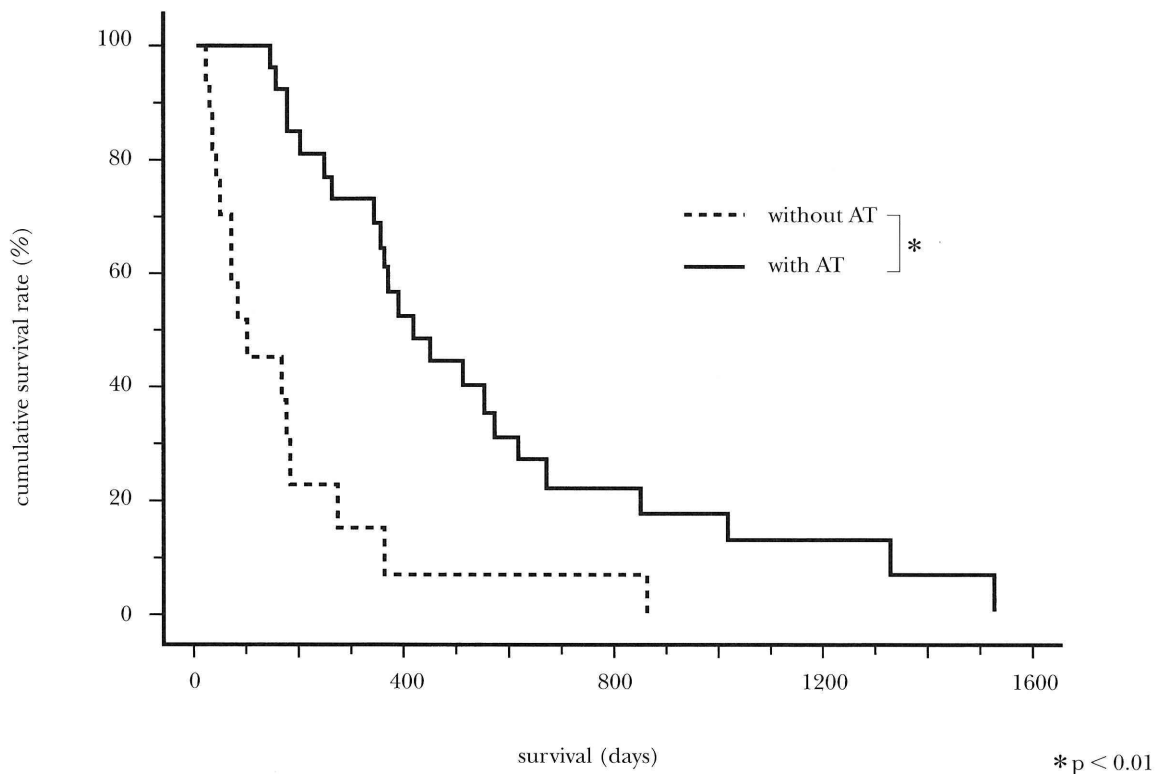


Fig. 2-b Cumulative survival rates of cholangiocarcinoma cases (upper biliary stricture) treated with or without adjunctive therapy. There was a significant difference between the two groups ($p < 0.01$). AT: adjunctive therapy

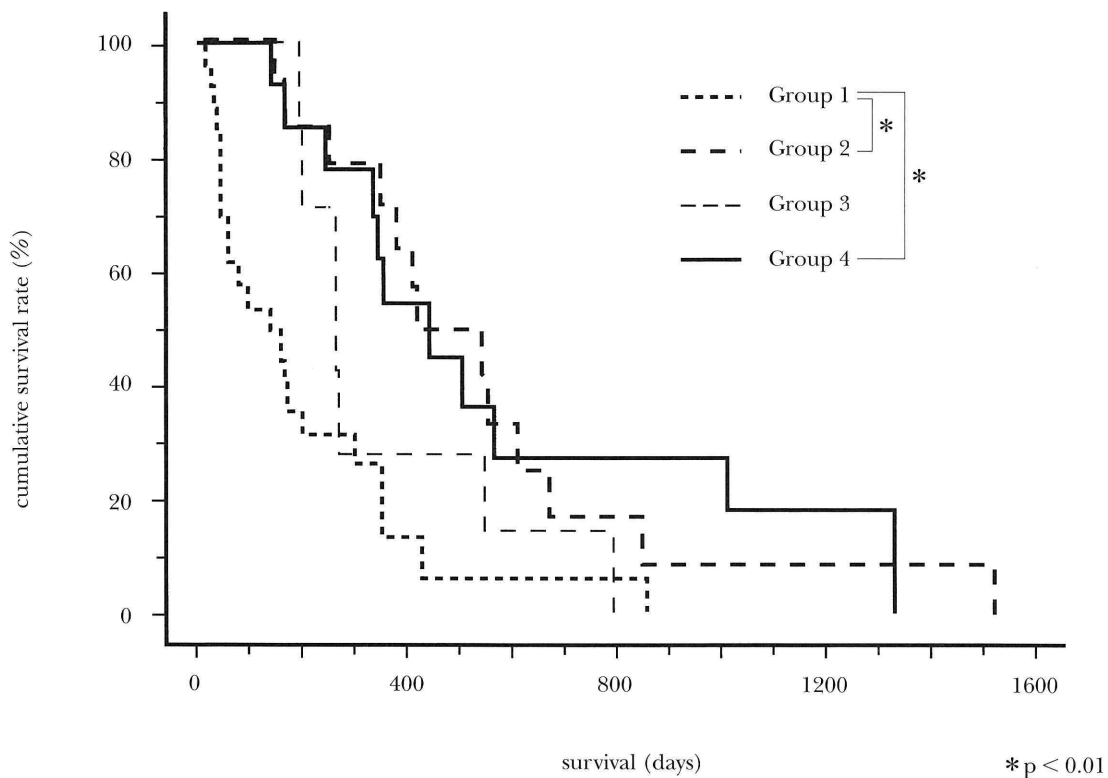


Fig. 2-c Cumulative survival rates of cholangiocarcinoma for adjunctive therapy group. A significant difference was seen between Group 1 and Group 2, Group 4. ($p < 0.01$). No significant difference was seen between Group 1 and Group 3. Group 1: No adjunctive therapy group. Group 2: External radiotherapy alone group. Group 3: Cholangial intraluminal therapy alone group. Group 4: External radiotherapy and cholangial intraluminal therapy group.

Table 3 Duration of hospitalization of cholangiocarcinoma in relation to adjunctive therapy and location of biliary tract stricture

	Upper stricture (n = 44)		Lower stricture (n = 21)	
	AT (+)(n = 27)	AT (-)(n = 17)	AT (+)(n = 10)	AT (-)(n = 11)
Median survival time (days)	510.3 ± 385.2	153.9 ± 103.9	329.1 ± 216.5	195.2 ± 142.3
Duration of hospitalization (days)	127.3 ± 115.9	79.1 ± 48.3	107.1 ± 42.0	48.2 ± 27.3

*p < 0.01, **p < 0.05, †NS, AT : Adjunctive therapy.

ment group (522.1 ± 426.8 days) than for the ERT group (206.6 ± 138.9 days) ($p < 0.01$).

5. Duration of Hospitalization

1) Duration of hospital stay in relation to adjunctive therapy

The duration of hospitalization was 60.6 ± 33.5 days for the group not receiving adjunctive therapy and 117.5 ± 84.8 days for the group receiving adjunctive therapy. The duration was significantly prolonged as a result of undertaking adjunctive therapy ($p < 0.01$).

2) Duration of hospitalization in relation to adjunctive therapy and by location of bile duct stricture (cholangiocarcinoma) (Table 3)

In lower bile duct stricture, there was a significant prolongation of hospital stay in patients receiving adjunctive therapy as compared with those receiving biliary drainage alone ($p < 0.01$). In upper bile duct strictures, no significant intergroup difference was observed.

3) Duration of hospitalization by type of adjunctive therapy (cholangiocarcinoma)

The duration of hospital stay was 146.5 ± 59.6 days for group 2, 114.0 ± 35.6 days for group 3, and 105.0 ± 43.5 days for group 4. Intergroup differences did not attain the level of statistical significance.

DISCUSSION

Nonsurgical biliary drainage is grossly classified into EBD and PTBD, for both of which internal biliary drainage has become feasible and is widely employed for unresectable malignant biliary strictures. However, the therapeutic benefit from biliary drainage is confined to improvement of cholestasis. In recent years, therefore, attempts have been made to

improve the survival time and prognosis by supplementing biliary drainage with various adjunctive therapies^{8~10}. The usefulness of these various adjunctive therapies, however, is yet to be clarified.

We considered it would be of importance in selecting biliary drainage approach procedures to determine the usefulness of adjunctive therapies. This is because most cholangial intraluminal therapies are performed only via a percutaneous transhepatic approach. Besides, it has been found that the local tumor control effect varied with target disease even if the same adjunctive therapy was given. The adjunctive therapy resulted in prolongation of treatment period.

In view of these, we evaluated the therapeutic effect of biliary drainage procedures, explored that of adjunctive therapies, and investigated selection of the most useful biliary drainage procedures for the treatment of unresectable malignant biliary stricture.

1. Therapeutic Effect in relation to Biliary Drainage Route

There should not be any difference in therapeutic effect between EBD as the transpapillary approach and PTBD as the percutaneous transhepatic approach insofar as the procedures provide external biliary drainage. However, there are several differences in therapeutic outcome between EBD and PTBD¹¹. The therapeutic success rate was lower with EBD (76.9%) than with PTBD (100%) in this study. It may be due to the technical skill of EBD is more difficult than that of PTBD. On the other hand, complications were more frequent with PTBD as compared to EBD.

With regard to jaundice-relieving effect, the

period until relief of jaundice was significantly shorter with EBD than with PTBD. Despite the general recognition that the larger the diameter of drainage tube, the greater the jaundice-relieving effect¹²⁾, the duration to relief of jaundice was shorter with ENBD using fine drainage catheters in the present study. This might probably be due to a shorter course of jaundice from its onset in the EBD group as compared to the PTBD group, although there was no appreciable difference in pre-drainage serum total bilirubin in the two groups. This is quite conceivable because EBD is performed even when the intrahepatic bile duct is only slightly dilated whereas PTBD is conducted after the intrahepatic bile duct is sufficiently dilated. Furthermore, there is the possibility that complications associated with the PTBD technique might affect the period to relief of jaundice. PTBD is considered to be accompanied more frequently with biliary tract hemorrhage, thereby prolonging the period to relief of jaundice, compared with EBD. As a biliary drainage procedure for unresectable malignant biliary strictures, EBD was considered superior to PTBD with respect to jaundice-relieving effect. However, one should be circumspect in prescribing EBD in cases of upper biliary stricture since the therapeutic outcome of EBD has been extremely poor in such cases. Moreover, local adjunctive therapy with biliary drainage is difficult when attempted via transpapillary approach¹²⁾ at present. Therefore, selection of the biliary drainage route should be based on not only the efficacy and procedural safety but also according to the site of stricture and whether any adjunctive therapy will be performed.

2. Adjunctive Therapy and Local Tumor Control Effect

Reports of studies concerning histologic evaluation of therapeutic responses, that is to what extent the tumor might be controlled by such adjunctive therapy, are extremely few as yet. Clinical responses to adjunctive therapy in carcinoma of the biliary tract and carcinoma of the pancreas have usually been evaluated according to the Evaluation Criteria for Treatment of Solid Tumors¹³⁾ and the Evaluation Criteria for Treatment of Biliary Tract Cancer¹⁴⁾, wherein the assessment of the effectiveness is based on tumor contraction rate esti-

mated from diagnostic imaging. These procedures eventually have involved such problems as difficulty in differentiating between fibrotic tissues resulting from therapy and residual cancerous tissues, thus tending to obscure the actual local control effect. We thus examined the local tumor control effect of the various adjunctive therapies in this study using cholangioscopically verified negative findings for malignancy as the primary endpoint.

Negative pathological findings for malignancy were obtained in only 25% of ERT-treated patients. Although increased radiation doses may probably elevate the local tumor control effect, it is generally thought that irradiation at 60 Gy and more by ERT alone is virtually impracticable¹⁵⁾, since the biliary tract is located deeply with contiguous intestines and liver which are relatively highly radiosensitive.

Most carcinomas of the biliary tract and those of the pancreas are poorly radiosensitive adenocarcinomas, and an external radiation dose of at least 80 Gy is required for radical treatment of adenocarcinoma. A 50–60 Gy dose by ERT, therefore, is considered to be theoretically inadequate for the control of tumor. Local tumor control effect rate for patients undergoing cholangial intraluminal therapy was 69.3%, which was better than with ERT. Of the 9 local control responders, 7 patients were treated by cholangioscopic therapy alone; suggesting good local tumor control effect of cholangioscopic therapy. A significant problem in this method is that it provides no effect at all against malignant lesions already spread to pericholangial regions.

IRT as a cholangial intraluminal therapy, on the other hand, may have therapeutic effects also against pericholangial infiltrative lesions and provide a greater local tumor control effect, compared to cholangioscopic therapy. According to Ryu et al, the local tumor control response rate was 62.5% when assessed by biopsy under cholangioscopic control after IRT with a total of 5-Gy dose given at 1.5 cm from the source¹⁶⁾.

Cholangioscopic therapy is considered more potent than IRT in providing the local tumor control effect, and may become a remarkably useful adjunctive therapy for papillary or nodular cholangiocarcinomas which are primarily located in the bile duct lumen. It is also possible to augment the local tumor control

effect of IRT by increasing the dose, but further study is needed to determine the optimal dose and exposure conditions because such dose increase may lead to an increase in incidence and severity of complications.

3. Adjunctive Therapy and Survival Time

There have been reports on radiotherapy^{7, 8)}, chemotherapy¹⁷⁾ and hyperthermia¹⁸⁾ as adjunctive therapies for unresectable malignant biliary strictures, but their prognosis-improving effect are unclear.

Primary diseases of malignant biliary stricture are mostly adenocarcinomas histologically, and the differences in local tumor control effect obtained might be attributable to differences in mode of spread and tumor bulk. Cholangiocarcinomas often present with obstructive jaundice even when they are still modest in size and produce distant metastases infrequently, hence the tumor bulk is considered relatively small even in unresectable cases. Carcinomas of the pancreas are liable to have distant metastases even when they are still relatively small, and are often recognized as overt masses on diagnostic imaging. Their bulkiness may account for their poorer responsiveness to adjunctive therapy than cholangiocarcinomas. In carcinomas of the gallbladder, it seems difficult to attain improvement of survival time by adjunctive therapy, since the tumor tends to infiltrate into the cholecystic bed and further into the liver relatively early. It may be said therefore that adjunctive therapy for malignant biliary stenosis should be chosen depending on the primary disease. This means that, in malignant biliary stricture, it is important to select a biliary drainage route based not only on the site of stricture but also on the the primary disease. And a biliary drainage approach should be selected primarily without regard to local adjunctive therapy but giving precedence to the jaundice-relieving effect and Quality of Life (Q.O.L.), in carcinomas of the gallbladder and carcinomas of the pancreas.

4. Cholangial Intraluminal Therapy for Cholangiocarcinoma

The adjunctive therapy we carried out proved to be effective in improving the survival time in patients with cholangiocarcinoma, but it remains unclear to what extent

ERT and cholangial intraluminal therapy contributed to the improvement of survival time.

In this study the survival time was improved in patients receiving ERT for treatment of cholangiocarcinoma, but no significant improvement of survival time was attained in patients receiving cholangial intraluminal therapy alone. This could be interpreted as implying that most of the patients studied had stage III or IV tumors and that the extent of spread itself was beyond the limits that could be covered by the effects of cholangial intraluminal therapy.

Ryu et al¹⁹⁾ have described that prolongation of survival could not be achieved by an increase in radiation dose in patients receiving IRT alone. The extended survival time seen in the present series, therefore, was considered ascribable to effective local control of tumor margins by adjunctive ERT. In the treatment of cholangiocarcinoma by ERT alone, the dose has reportedly been 50–60 Gy in most cases.

In this study, we observed no significant difference in survival time between ERT at 50–60 Gy alone and ERT at 20–30 Gy plus cholangial intraluminal therapy. Yamada et al²⁰⁾ have reported gratifying results from IRT plus ERT at 20 Gy, that is a local control rate of 90% and a three-year survival rate of 17%. In other words, it was possible to attain a survival time similar to that by ERT alone, in patients receiving nearly half the dose of ERT alone when cholangial intraluminal therapy was concurrently undertaken.

The scheduled dose of radiation sometimes cannot be accomplished in high-dose ERT because of adverse reactions, thereby failing to obtain improvement in outcome. In contrast, the adverse reaction seen with ERT are remarkably rare with cholangial intraluminal therapy. Therefore, cholangial intraluminal therapy is considered to be useful when performed in combination with ERT, since it may enable accomplishing scheduled radiation and improve the survival time while reducing the occurrence of adverse reactions.

Obstructive jaundice and cholangitis arising from bile duct stricture, besides spread of the underlying malignant tumor, have substantial bearing on the outcome in cases of unresectable malignant biliary strictures. In the cases of upper biliary strictures where several

bile duct branches are divided into segments owing to advancing malignant growth, prevention of such bile duct segmentation by potent local adjunctive therapy may contribute to improvement of outcome as well as to prophylaxis of recurrent jaundice and cholangitis.

There has been a report showing a significantly longer survival time for a group of patients with unresectable cholangiocarcinoma receiving percutaneous transhepatic biliary endoprosthesis (PTBE), an internal fistulation of PTBD, compared with a group receiving PTBD²¹⁾. This prolongation has been attributed to the greater advantages of the former with respect to nutrition and metabolism²¹⁾.

The duration for which the internal biliary drainage was maintained intact was significantly longer for the group receiving adjunctive cholangial intraluminal therapy in the present study. This was considered to be a result of inhibition of progress of bile duct branch strictures by local control of the tumor lesion and inhibition of bile sludge in and outside a stent due to a reduction in microbleeding from the tumor. With the adjunctive cholangial intraluminal therapy, the stenosis is fully dilated thus permitting placement of stents with relatively large diameters, and this may probably constitute a factor for the rarity of intercurrent cholangitis.

5. Adjunctive Therapy and Duration of Hospitalization

A major problem in adjunctive therapy is prolongation of treatment duration. It is of enormous importance to decide how much to reduce the proportion of treatment duration in the remaining survival time since most of the patients are suffering unresectable malignant lesions and probably have a short survival time left. In the present study, a significant extension of initial hospital stay was noted in patients receiving adjunctive therapy. When survival time and duration of hospitalization were compared for individual clinical entities, it was noted that, in cholangiocarcinoma, the total stay was prolonged and the survival time was also extended. In carcinomas of the pancreas and the gallbladder, however, no prolongation of the survival time commensurate with extension of hospital stay could be obtained.

The length of hospitalization substantially affects the Q.O.L. of the patients whose remaining survival time is estimated to be relatively short. It is considered quite meaningful therefore, to evaluate adjunctive therapy in the light of prolongation of hospitalization and improvement of survival time. For cholangial intraluminal therapy particularly, hospitalization for the treatment has usually been essential due to technical factors.

We have devised an applicator for IRT, and perform the procedure at the outpatient clinic in most cases with maintained internal biliary drainage, so as to further reduce the duration of hospital stay.

Cholangioscopic therapy, on the other hand, is still difficult to perform on outpatients under present conditions. We perform cholangioscopic therapy during the hospital course of treatment for relief of jaundice and subsequently undertake IRT or ERT or both at outpatient clinic. The currently available adjunctive therapies, however, were not considered to be reliably effective in carcinomas of the pancreas and of the gallbladder even from the viewpoint of effectiveness prolonged treatment duration. For the treatment of malignant strictures due to carcinoma of the pancreas or carcinoma of the gallbladder, therefore, selection of approach routes would have to be made giving precedence to the benefit of biliary drainage and the fewer limitations related to the drainage technique, hence without regard to adjunctive therapy for the local control of the tumor.

CONCLUSION

In the treatment of unresectable malignant biliary strictures, the percutaneous transhepatic approach permitting cholangial intraluminal therapy should be undertaken for cholangiocarcinoma and the less invasive transpapillary approach with a shorter treatment duration should be selected for carcinoma of the pancreas. For carcinoma of the gallbladder, selection of a drainage approach should be based on site of stricture and prior estimation of the prognosis.

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切除不能悪性胆道狭窄に対する胆道ドレナージルート の選択と併用療法の検討

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切除不能悪性胆道狭窄に対する胆道ドレナージ術と各種併用療法の成績について検討した。対象は1986年6月より1998年5月までに当科で経験した悪性胆道狭窄のうち、予後の明らかな135例である。アプローチ別に胆道ドレナージの成績を比較すると、経乳頭的ドレナージは経皮経肝のドレナージと比較して、減黄期間については有意に短期間で合併症頻度も少なかったが、手技的な成功率はやや劣り、また胆道狭窄の部位が上位である場合の減黄成績は極めて不良であった。

併用療法の胆管内腔制御効果について胆道鏡下生検により組織学的に検討すると、放射線体外照射と比較して胆管腔内治療が極めて優れていた。併用療法の付加による生存期間の改善効果は、胆管癌では有意に生存期間の改善が得られた。しかし膵臓癌では生存期間の改善効果は胆管癌に比べてやや乏しく、胆嚢癌においては全く改善が得られていなかった。複数の胆管狭窄がみられる上位胆管狭窄における内瘻維持期間は、胆管腔内治療の付加により著しく延長し、いわゆる Quality of life の向上にも胆管腔内治療は有用であった。一方、併用療法の付加による入院治療期間は、胆道ドレナージのみを施行した群に比べて有意に延長しており、治療期間の延長に見合う生存期間の改善が期待し得ない場合には、胆道ドレナージの付加にとどめるべきと考えられた。

以上より、切除不能悪性胆道狭窄に対する治療法の選択は、胆管癌では胆管腔内治療が施行可能な経皮的アプローチによる胆道ドレナージを行い、可能な限り併用療法を施行すべきである。一方、併用療法の有用性が明らかでない膵臓癌と胆嚢癌については胆道ドレナージの施行にとどめることが望ましく、膵臓癌では経乳頭的アプローチを選択し、胆嚢癌では狭窄部位により経皮的アプローチと経乳頭的アプローチを適宜選択すべきである。

キーワード：悪性胆道狭窄，胆道ドレナージ，放射線治療，体腔内放射線治療，胆道内視鏡下治療
