



## Original article

# Efficacy and safety of therapeutic endoscopic retrograde cholangiopancreatography in patients with native papillae with a performance status score of 3 or 4: A single-center retrospective study

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## Abstract

**Objective:** This study aimed to assess the efficacy and safety of therapeutic endoscopic retrograde cholangiopancreatography (ERCP) in patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 3 or 4.

**Patients and Methods:** We reviewed the data of 287 patients with native papillae who underwent therapeutic ERCP for biliary disease at our hospital between October 2016 and October 2018. The patients were divided into two groups; those with an ECOG-PS score of 3 or 4 (group A; n=78) and those with an ECOG-PS score of 0–2 (group B; n=209).

**Results:** The rate of technical success was not significantly different between the two groups (95% versus 89%,  $P=0.13$ ). Although the occurrence rate of overall adverse events (10% versus 11%,  $P=0.95$ ) was not significantly different between the groups, the occurrence rates of aspiration pneumonia (3.8% versus 0%,  $P=0.0044$ ) and heart failure (2.6% versus 0%,  $P=0.020$ ) were significantly higher in group A.

**Conclusion:** The rates of technical success and overall adverse events did not significantly differ between patients with an ECOG-PS score of 3 or 4 and those with a score of 0–2; however, aspiration pneumonia and heart failure were more likely to occur among patients with an ECOG-PS score of 3 or 4.

**Key words:** adverse event, endoscopic retrograde cholangiopancreatography, Eastern Cooperative Oncology Group performance status score, technical success

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## Introduction

As aging populations continue to increase worldwide and the number of elderly persons with biliary disease increases, and the number of elderly patients undergoing therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is also increasing<sup>1</sup>. In elderly patients, the level of activities

of daily living is often declining. The Eastern Cooperative Oncology Group performance status (ECOG-PS) score<sup>2</sup>, originally used in patients with cancer, is an objective indicator of the level of activities of daily living. Although ERCP is an important approach for the treatment of biliary disease, the impact of the ECOG-PS score on therapeutic ERCP outcomes remains unclear. A retrospective study of 281 elderly patients who underwent ERCP showed that an ECOG-PS score of 3 or 4 was not a risk factor for serious adverse events<sup>3</sup>. In this study, we assessed the efficacy and safety of therapeutic ERCP in patients with native papillae with an ECOG-PS score of 3 or 4.

## Patients and Methods

This was a single-center, retrospective study. Patients with native papillae who underwent therapeutic ERCP for biliary disease at the Mito Saiseikai General Hospital be-

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tween October 2016 and October 2018 were considered eligible for inclusion in this study. The exclusion criteria were ERCP for diagnostic purposes only, inability of the scope to reach the duodenal papillae, and ERCP for gallbladder disease. This study was approved by the institutional review board of the Mito Saiseikai General Hospital.

Of the 297 patients who were eligible for inclusion, 5 patients who underwent ERCP for diagnostic purposes only, 1 patient in whom the scope did not reach the duodenal papillae, and 4 patients who underwent ERCP for gallbladder disease were excluded from the study. Therefore, 287 eligible patients (158 men and 129 women) were finally included in this study.

The eligible patients were divided into two groups; those with an ECOG-PS score of 3 or 4 (group A) and those with an ECOG-PS score of 0–2 (group B). To determine the ECOG-PS score, we referred to the patients' medical records at hospitalization. At the time of admission of the patients, the levels of activities of daily living based on the daily situation in the past week were recorded by medical staff at our hospital. And, the baseline characteristics and clinical outcomes were obtained from the patients' medical records. The baseline characteristics included ECOG-PS score, age, sex, indication for ERCP, frequency of emergency procedures, frequency of involvement of a trainee endoscopist in the procedure, frequency of comorbid cholangitis, frequency of dialysis, intake of an anticoagulant drug, presence of a juxtapaillary duodenal diverticulum, American Society of Anesthesiologists physical status classification (ASA-PS)<sup>4</sup>, and Charlson Comorbidity Index (CCI)<sup>5</sup>. The clinical outcomes included the technical success rate, type of treatment procedure, presence of a sphincterotomy, administered dose of pentazocine, administered dose of midazolam, procedure time, and adverse events.

Technical success was defined as a successful cannulation of the bile duct and a completed procedure (stenting, endoscopic nasobiliary drainage placement, endoscopic naso-gallbladder drainage, or stone removal), regardless of procedural difficulty. The procedure time was defined as the time interval between the insertion of the endoscope into the mouth and its removal. In this study, a trainee was defined as an endoscopist who had performed <300 ERCPs. In most cases, ERCP was performed by a team including a trainee and an expert. Adverse events were evaluated according to the definitions for endoscopic adverse events in the American Society for Gastrointestinal Endoscopy workshop report<sup>6</sup>.

ERCP was performed through therapeutic duodenoscopy (JF 260 V; Olympus, Tokyo, Japan), and carbon dioxide insufflation was used unless contraindicated. Anesthesia induction was not assisted by an anesthesiologist and was performed by gastroenterologists. Before the procedure, intravenous sedation was achieved with 15 mg pentazocine and

2.0–5.0 mg midazolam. Additional doses were administered as needed. Intravenous butylscopolamine bromide or glucagon was also administered to inhibit intestinal motility. Two hours after the procedure, 20 mg nafamostat mesilate was administered intravenously. For antibiotic prophylaxis, 1 g cefoperazone-sulbactam was administered intravenously 1 h before and 4 h after ERCP.

Before ERCP, antithrombotic agents were managed according to the Japan Gastroenterological Endoscopy Society guidelines<sup>7</sup>, except for emergency cases. Oral antithrombotic drug administration was continued in patients who were not expected to undergo sphincterotomy. Among patients expected to undergo a sphincterotomy, the regimen was continued in those receiving one antiplatelet agent; however, in those receiving multiple antiplatelet agents, only one antiplatelet agent was continued. Patients who were administered oral anticoagulants underwent heparinization, which was stopped 4–6 h before therapeutic ERCP.

## Statistical analysis

Data are presented as mean with standard deviation or number with percentage. For univariate analysis, the Mann-Whitney *U*-test was used to compare continuous variables and Pearson's  $\chi^2$  test was used to compare categorical variables. All statistical analyses were performed using Bell-Curve for Excel (Social Survey Research Information, Tokyo, Japan).

## Results

The ages of the 287 eligible patients ranged from 19 to 98 years, with a mean of 74.1 (13.8) years. The number of patients was 78 in group A and 209 in group B. Table 1 shows a comparison of the background characteristics of each group. Age [83.9 (8.1) years versus 70.5 (13.7) years,  $P < 0.001$ ], proportion of women (62% versus 39%,  $P = 0.0006$ ), proportion of patients undergoing dialysis (9.0% versus 3.3%,  $P = 0.049$ ), ASA-PS [2.0 (0.6) versus 1.8 (0.6),  $P = 0.018$ ], and CCI [1.7 (1.2) versus 1.2 (1.1),  $P = 0.0037$ ] were significantly higher in group A than in group B. There was no significant difference in other baseline characteristics between the groups.

Table 2 shows a comparison of the treatment outcomes. The rate of technical success (95% versus 89%,  $P = 0.13$ ) was not significantly different between the groups. Moreover, both the administered dose of pentazocine [6.8 (7.4) mg versus 11.3 (6.6) mg,  $P < 0.001$ ] and the administered dose of midazolam [4.2 (1.6) mg versus 5.6 (2.2),  $P < 0.001$ ] were significantly less among patients in group A than in those in group B. The procedure time was significantly shorter in patients in group A than in those in group B [33.1 (14.3) versus 37.8 (15.9),  $P = 0.016$ ]. Although the occurrence rate of overall adverse events (10% versus 11%,  $P = 0.95$ ) was not significantly different, the occurrence rates of aspiration pneu-

**Table 1** Baseline characteristics and medical history of eligible cases

	ECOG-PS score 3 or 4 n=78	ECOG-PS score 0–2 n=209	P-value
ECOG-PS score, mean (SD)	3.4 (0.5)	0.6 (0.8)	< 0.001
0, n (%)	0	124 (59%)	
1, n (%)	0	51 (24%)	
2, n (%)	0	34 (16%)	
3, n (%)	47 (60%)	0	
4, n (%)	31 (40%)	0	
Age, mean (SD)	83.9 (8.1)	70.5 (13.7)	< 0.001
Women, n (%)	48 (62%)	81 (39%)	< 0.001
Indication, n (%)			
Biliary stone	55 (71%)	138 (66%)	0.47
Extrahepatic cholangiocarcinoma	8 (10%)	25 (12%)	0.69
Gallstone pancreatitis	7 (9.0%)	21 (10%)	0.79
Pancreatic cancer	4 (5.1%)	14 (6.7%)	0.63
Gallbladder cancer	3 (3.8%)	5 (2.4%)	0.51
Duodenum papillary cancer	1 (1.3%)	4 (1.9%)	0.72
Intrahepatic cholangiocarcinoma	0	2 (0.96%)	0.39
Emergency, n (%)	33 (42%)	90 (43%)	0.91
Involvement of a trainee, n (%)	77 (99%)	206 (99%)	0.92
Cholangitis, n (%)	50 (64%)	110 (53%)	0.082
Dialysis, n (%)	7 (9.0%)	7 (3.3%)	0.049
Antithrombotic drug, n (%)	29 (37%)	55 (26%)	0.072
Juxtapapillary duodenal diverticulum, n (%)	30 (38%)	68 (33%)	0.35
ASA physical status classification, mean (SD)	2.0 (0.6)	1.8 (0.6)	0.018
Charlson comorbidity index, mean (SD)	1.7 (1.2)	1.2 (1.1)	0.0037

ECOG-PS: Eastern Cooperative Oncology Group performance status score; SD: standard deviation; ASA: American Society of Anesthesiologists.

**Table 2** Clinical outcomes of eligible cases

	ECOG-PS score 3 or 4 n=78	ECOG-PS score 0–2 n=209	P-value
Technical success, n (%)	74 (95%)	186 (89%)	0.13
Procedure time (min), mean (SD)	33.1 (14.3)	37.8 (15.9)	0.016
Sphincterotomy performance, n (%)	54 (69%)	153 (73%)	0.50
Administered dose of pentazocine (mg), mean (SD)	6.8 (7.4)	11.3 (6.6)	< 0.001
Administered dose of midazolam (mg), mean (SD)	4.2 (1.6)	5.6 (2.2)	< 0.001
Procedure, n (%)			
Biliary stenting	56 (72%)	127 (61%)	0.084
Stone removal	17 (22%)	47 (22%)	0.90
Endoscopic nasobiliary drainage	1 (1.3%)	12 (5.7%)	0.11
Failure	4 (5.1%)	23 (11%)	0.13
Adverse event, n (%)	8 (10%)	22 (11%)	0.95
Pancreatitis	3 (3.8%)	16 (7.7%)	0.25
Cholangitis	0	4 (1.9%)	0.22
Aspiration pneumonia	3 (3.8%)	0	0.0044
Heart failure	2 (2.6%)	0	0.020
Post-sphincterotomy hemorrhage	0	1 (0.48%)	0.54
Cardiac arrest	0	1 (0.48%)	0.54

ECOG-PS: Eastern Cooperative Oncology Group performance status score; SD: standard deviation.

monia (3.8% versus 0%,  $P=0.0044$ ) and heart failure (2.6% versus 0%,  $P=0.020$ ) were significantly higher in group A than in group B. One patient died of aspiration pneumonia and another died of heart failure after ERCP; however, all other patients with adverse events showed improvements. In two patients who developed pneumonia, the dose of pentazocine was 15 mg in both patients and the dose of midazolam was 4 and 5 mg in each patient.

Of the 78 patients in group A, 3 patients (3.8%) died within the first 30 days after ERCP (1 due to aspiration pneumonia, 1 due to heart failure after ERCP, and 1 due to progression of malignant disease). Of the 209 patients in group B, 5 patients (2.4%) died within the first 30 days of ERCP, and all deaths were due to progression of the malignant disease. Therefore, the overall 30-day mortality rate was 2.8% (8 of 287 patients). The overall ERCP-related 30-day mortality rate was 0.70% (2 of 287 patients); 2.6% (2 of 78 patients) in group A and 0% (0 of 209 patients) in group B ( $P=0.020$ ). There was no obvious sedation-related death.

## Discussion

This study revealed no significant difference in the rate of technical success or overall adverse events in patients with native papillae who underwent therapeutic ERCP, regardless of the ECOG-PS scores. However, the rates of aspiration pneumonia and heart failure, and the ERCP-related mortality rate were significantly higher among patients with scores of 3 or 4 than among those with scores of 0–2.

According to several previous reports on the safety of ERCP in elderly patients<sup>8–14</sup>, the procedure can be performed effectively and safely in a majority of elderly patients. However, there are few reports on the relationship between the ECOG-PS score and the efficacy and safety of ERCP in patients with native papillae<sup>3</sup>. According to another previous study, ECOG-PS scores of 3 or 4 do not indicate a higher risk for serious adverse events<sup>3</sup>; however, the efficacy, safety, and other characteristics of ERCP in patients with native papillae with an ECOG-PS score of 3 or 4 have not been adequately studied.

The results of this study indicated that the incidence of aspiration pneumonia and heart failure was significantly higher among patients with ECOG-PS scores of 3 or 4. Therefore, particularly in such patients, care must be taken to prevent aspiration pneumonia and heart failure. To prevent aspiration pneumonia, oral care before ERCP can be effective. Moreover, particularly in emergency cases, it is important to examine how much food remains in the stomach, and to confirm the time of the last meal and the diet contents in detail. To prevent heart failure, it is desirable to evaluate cardiac function with echocardiography and adjust the volume of infusion accordingly. The depth of sedation may also be related to the development of aspiration pneumonia.

Although a clear relationship between sedation and adverse events could not be proved in this study, it was possible that sedation contributed to the development of aspiration pneumonia. In this study, the administered doses of pentazocine and midazolam were significantly less among patients with ECOG-PS scores of 3 or 4. A retrospective study reported that the risk of sedation-related adverse events is increased in elderly patients undergoing ERCP<sup>15</sup>. In this study, the dose of pentazocine in two patients who developed pneumonia was higher than mean dose. Attention should be paid to the amount of sedatives, particularly pentazocine, used in patients with ECOG-PS scores of 3 or 4.

The procedure time was significantly shorter among patients with ECOG-PS scores of 3 or 4, which may be due to the avoidance of difficult procedures in these patients. The results might change if the conditions of procedural difficulty are matched in each group. Further, on the basis of the results of this study, the ERCP-related 30-day mortality rate increased among patients with ECOG-PS scores of 3 or 4. ASA and CCI were significantly higher among patients with ECOG-PS scores of 3 or 4, which may have been related to the higher ERCP-related 30-day mortality rate. Prospective studies are needed to verify the efficacy and safety of therapeutic ERCP in patients with native papillae with ECOG-PS scores of 3 or 4.

This study has several limitations. First, this was a retrospective study performed at a single center, and data from only a small number of patients were included in the final analyses. Second, we statistically evaluated all kinds of adverse events in a collective manner. As there were significant differences depending on the type of adverse event, the results might change if the overall number of patients increases. Third, with respect to technical success, we did not consider the difficulty of the procedures. Procedures with a high degree of difficulty might be avoided more for patients with ECOG-PS scores of 3 or 4 than for patients with good ECOG-PS scores. Finally, we did not match the background characteristics of the two groups. If background matching was done, different results might have been obtained.

## Conclusion

In patients with native papillae who underwent therapeutic ERCP for biliary disease, the rates of technical success and overall adverse events did not differ significantly between those with ECOG-PS scores of 3 or 4 and those with ECOG-PS scores of 0–2. However, aspiration pneumonia and heart failure were more likely to occur among patients with ECOG-PS scores of 3 or 4 than among those with ECOG-PS scores of 0–2. In addition, the ERCP-related 30-day mortality rate increased in patients with ECOG-PS scores of 3 or 4 than in those with ECOG-PS scores of 0–2.

**Conflict of interest:** The authors declare that there are no conflicts of interest.

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