【 ORIGINAL ARTICLE 】

Long-term Outcomes of Therapeutic Endoscopic Retrograde Cholangiopancreatography for Choledocholithiasis in Patients ≥90 Years Old: A Multicenter Retrospective Study

Shinya Sugimoto[1], Aiji Hattori[2], Yuri Maegawa[3], Haruka Nakamura[1], Naoko Okuda[1],
Toshifumi Takeuchi[3], Jun Oyamada[1], Akira Kamei[1], Hiroyuki Kawabata[2],
Masatoshi Aoki[2] and Hiroaki Naota[3]

Abstract:

Objective The safety and prognosis of complete stone removal for the treatment of choledocholithiasis in older patients are unknown. This multicenter retrospective study assessed the outcomes of complete stone removal in elderly patients (≥90 years) with respect to the prognosis.

Methods We divided patients who underwent endoscopic cholangiopancreatography for choledocholithiasis into two groups: complete stone removal or incomplete stone removal with plastic stent insertion. The patient characteristics, adverse events, number of endoscopic cholangiopancreatographies, overall survival rates, and disease-specific cumulative death were compared between the groups.

Patients Two hundred and twenty-three participants ≥90 years old were included in the study, including 48 (22%) men and 175 (78%) women. The median age was 92 (range, 90-104) years old. There were 160 (72%) and 63 (28%) patients in the complete and incomplete groups, respectively.

Results The age, performance status, comorbidities, severe complication rates, and stone diameter were comparable between the groups. The proportion of patients with at least 5 stones was significantly higher in the incomplete group than in the complete group [complete group: 8.1% (13/160) and incomplete group: 21% (13/63), p<0.01]. The overall survival rate was significantly higher in the complete group (p<0.01), while the disease-specific cumulative death rate was higher in the incomplete group (p<0.01).

Conclusion Complete stone removal for choledocholithiasis may contribute to a better prognosis in elderly patients ≥90 years old.

Key words: biliary tract, choledocholithiasis, elderly, endoscopic cholangiopancreatography, stone removal, survival rate

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Introduction

The World Health Organization Health Report has noted the issue of global aging (1). The prevalence of gallbladder and bile duct stones rises with age (2-4), while postoperative morbidity and mortality increase with age and the presence of comorbidities.

Endoscopic retrograde cholangiopancreatography (ERCP) is an established diagnostic and therapeutic approach for pancreaticobiliary diseases, such as choledocholithiasis. However, ERCP is also associated with risks; it has a reported adverse event rate of 5-10% and a mortality rate of 0.3-0.5% (5-7). Furthermore, these risks may be exacerbated by age; thus, their consequences may be more severe and protracted in elderly patients than in younger ones. Several

studies have reported that complete stone removal for chole-docholithiasis is safe (8) and may contribute to a good prognosis (9), even in older patients. Although biliary stent insertion may be a viable alternative to complete stone removal in high-risk patients, the long-term outcomes remain a concern (10-13). To our knowledge, few studies have assessed the need for complete stone removal for choledocholithiasis in patients of advanced age (≥90 years old) with regard to their prognosis.

We previously reported that complete stone removal in choledocholithiasis did not contribute to a better prognosis in patients of advanced age; however, the insufficient number of patients limited the drawing of firm conclusions (14). Therefore, in this multicenter retrospective study, we assessed the safety and necessity of complete stone removal in elderly patients with choledocholithiasis.

Materials and Methods

Participating institutions

This multicenter retrospective cohort study included three institutions (Ise Red Cross Hospital, Saiseikai Matsusaka General Hospital, and Matsusaka Chuo General Hospital) in Mie Prefecture, Japan. All institutions are members of the Japan Gastroenterological Endoscopy Society. The study protocol adhered to the ethical principles of the Declaration of Helsinki and was approved by the ethics committee of each institution. Written informed consent was obtained from all patients before ERCP.

Study population

In this study, we initially enrolled 233 consecutive patients ≥90 years old who underwent ERCP for choledocholithiasis diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) at participating institutions between January 2012 and December 2018.

Ten patients were excluded from the analysis, and six of them had a surgically altered anatomy (due to total gastrectomy in one and Billroth II stomach reconstruction by distal gastrectomy in five). The other four patients, who died of cholangitis, had severe comorbidities including pneumonia in two, sick sinus syndrome in one, and heart failure in one. They were considered ineligible for this study because their comorbidities might have affected their prognosis.

A total of 223 patients (435 ERCP procedures) were included in the final analysis. The patients were divided into two groups: complete stone removal group (C group; underwent complete stone removal) and incomplete stone removal group (I group; did not undergo complete stone removal but underwent plastic stent insertion). Patients who underwent complete stone removal after transient biliary stenting were assigned to group C. In addition, in the C group, complete stone removal was initially judged as difficult in eight patients, so they were not scheduled for complete stone removal. However, the stones in these patients subsequently shrank in size, eventually enabling complete stone removal during the follow-up period (Fig. 1). The patient characteristics, adverse events, number of ERCP procedures, and long-term survival rates were compared between the two groups.

Sedation procedure

All patients were monitored continuously for oxygen saturation, heart rate, and blood pressure during ERCP. Each patient received oxygen (2 L/min) through a nasal cannula. Patients were initially injected with midazolam (1-3 mg) for sedation and then received meperidine (5-10 mg) or pentazocine (7.5-15 mg) intravenously for analgesia. Additional doses of midazolam (1 mg), meperidine (5 mg), and pentazocine (7.5-15 mg) were administered intermittently during the procedure as needed.

There was no special protocol for older patients; however, the dosage and frequency of each bolus were adjusted according to the age and comorbidities. At all participating institutions, sedation was performed by an endoscopist.

Endoscopic procedure

After confirming that the patients were adequately sedated, ERCP was performed using a side-viewing endoscope (JF-260 V and TJF-260 V; Olympus Medical Systems, Tokyo, Japan). The common bile duct (CBD) was selectively imaged, and the size and number of stones were confirmed. Endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), endoscopic papillary large balloon dilation (EPLBD), or plastic stent insertion was performed based on the operator's decision. For removal of bile duct stones, a retrieval balloon catheter or stone extraction basket was used. When stenting the bile duct, we used a 7-Fr pigtail stent (Zimmon®; Cook Ireland, Limerick, Ireland), a 7- to 8.5-Fr straight stent (Flexima™; Boston Scientific Japan, Tokyo, Japan), or an 8.5-Fr stent (Soehendra Tannenbaum®; Cook Medical, Bloomington, USA). Following endoscopic stone removal, the procedure was considered successful when no remaining radiolucent stones were visible on contrast-enhanced imaging.

All participating endoscopists agreed that complete stone removal was the standard, targeted, and recommended strategy for treating choledocholithiasis, even in elderly patients. However, the three participating institutions lacked unified criteria for abandoning complete stone removal and converting to stent insertion. In addition, all ERCP procedures were supervised by 6 well-experienced endoscopists (AK, JO, SS, HN, MA, and HK) who had each performed >1,000 ERCP procedures.

We previously reported the long-term outcomes of therapeutic ERCP for choledocholithiasis in patients ≥90 years old in a single institution (14). The above-mentioned ERCP procedures were conducted as previously described (14).

Definition of complications

Complications during endoscopy were defined as ERCP-and/or sedation-related adverse events, including the follow-
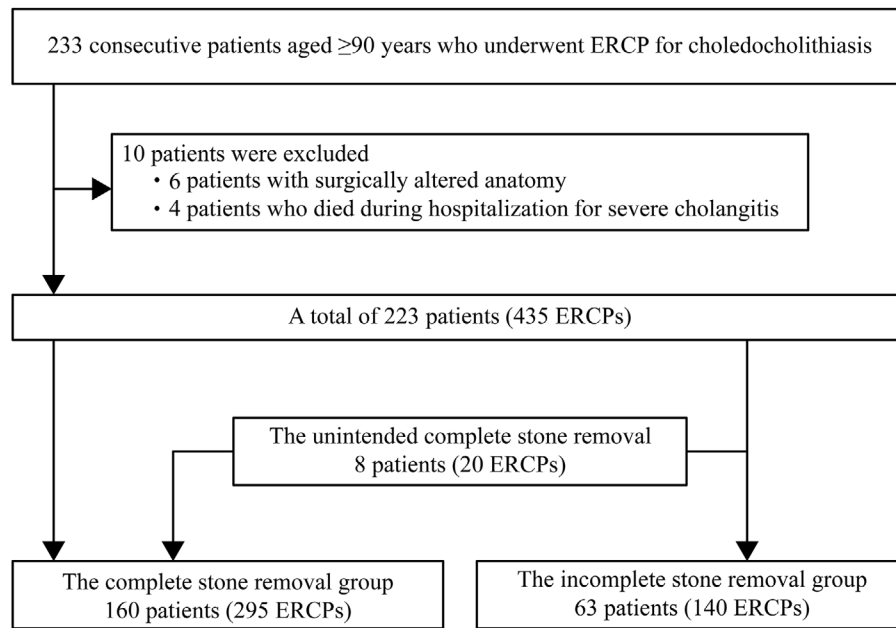
Figure 1. Flowchart displaying the patient enrollment process. ERCP: endoscopic retrograde cholangiopancreatography

ing: hypoxemia (oxygen saturation <90%), hypotension (systolic blood pressure <90 mmHg), and bradycardia (heart rate <50 bpm). Perforation was defined as retroperitoneal or bowel wall perforation detected by any imaging technique. The occurrence of post-ERCP pancreatitis (PEP) and its severity were assessed according to the 1991 consensus guidelines, as specified by Cotton et al. (15).

Follow-up after ERCP

After ERCP, a protease inhibitor was administered to prevent pancreatitis (16, 17). All patients underwent a routine follow-up investigation with laboratory testing after ERCP. For patients with abdominal pain, the serum amylase level was measured, and abdominal CT was performed if the symptoms persisted.

After discharge, patients were scheduled to visit our outpatient clinic or were referred to their family doctor. We asked their family doctor to refer them to our hospital if biliary tract infection (cholangitis, cholecystitis, or liver abscess) was suspected. In such cases, laboratory tests, abdominal CT, and then ERCP, if necessary, were performed. In this study, planned regular stent exchange is not a standard strategy in participating institutions.

In this study, we evaluated the overall survival (OS) and disease-specific survival (DSS) to determine the need for complete stone removal in patients of advanced age with regard to their prognosis. The survival time for all patients was calculated from the date of initial ERCP to the date of the final survival confirmation.

Disease-specific death was defined as death associated with biliary tract infection due to either retrograde biliary infection, stent occlusion/shedding, or stone recurrence or as death due to uncontrollable bleeding, perforation, or other complications associated with ERCP. All long-term follow-up data were collected by communicating with family doctors of patients, from outpatient notes, or through phone calls to patients' homes. The follow-up period started from the first date of ERCP to the date of the last visit to the patient's family doctor or our outpatient clinics, or upon confirmation of the survival through a phone call.

Measured outcomes of therapeutic ERCP

The evaluation outcomes were the total number of procedures, number and size of biliary stones, procedure time, endoscopic procedure (EST, EPBD, and/or EPLBD), rate and type of complication, causes of death, and OS and DSS. The total number of procedures was defined as all endoscopic procedures required for complete stone removal, recurrent stones, and retrograde cholangitis in C group and for stent exchange due to biliary tract infection for stent dysfunction in I group during the follow-up period. The number of biliary stones was confirmed using cholangiography, and the diameter of the stones was measured with reference to the diameter of the endoscope. The procedure time was defined as the amount of time required from the insertion to the removal of the endoscope. EPLBD was defined as mechanical dilation of the major duodenal papilla using a balloon with a diameter ≥12 mm. The OS rate was defined as the percentage of included patients who remained alive at the date of the final survival confirmation, and the DSS rate was defined as the percentage of included patients who did not die from biliary tract infection (cholangitis, cholecystitis, or liver abscess) from the date of initial ERCP to the date of the final survival confirmation.

Table 1.   Patient Characteristics.

	Complete stone removal (n=160)	Incomplete stone removal (n=63)	p value
Sex, male: female	39:121	9:54	0.11*
Age, years, mean	92.8	92.7	0.97**
Performance status, mean	2.5	2.8	0.11*
Comorbidities, % (n)			
Coronary heart disease	11.9 (19/160)	19.0 (12/63)	0.20*
Respiratory disease	5.0 (8/160)	7.9 (5/63)	0.53*
Cerebrovascular disease	11.9 (19/160)	25.4 (16/63)	0.12*
Renal failure with dialysis	3.1 (5/160)	0 (0/63)	0.33*
Dementia	34.4 (55/160)	50.8 (32/63)	0.03*
Use of antithrombotic drugs, % (n)	27.5 (44/160)	34.9 (22/63)	0.35*
Cholangitis, % (n)	66.3 (106/160)	73.0 (46/63)	0.41*
Patients with naive papillae, % (n)	87.5 (140/160)	96.8 (61/63)	0.03*

*Fisher's exact test, ** Student's *t*-test.

Statistical analyses

Continuous variables are presented as the mean values, whereas categorical variables are reported as patient numbers and percentages. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test, and categorical variables were compared using Fisher's exact tests, as appropriate. To describe the OS, we used Kaplan-Meier estimates of survival curves and fitted a Cox proportional hazard model. In addition, we used Gray's test to analyze the DSS. Specifically, we investigated the cumulative incidence (death in this case) caused by biliary events versus non-biliary events with respect to the C and I groups.

Statistical significance was set at p<0.05. For all statistical analyses, we used the R environment for statistical computing and graphics (R Core Team, 2017) (18), with the graphical user interface "EZR" (Easy R) (19).

Results

Patient characteristics

The study population comprised 48 men (21.5%) and 175 (78.5%) women. The median age at the time of the first ERCP procedure was 92 (range, 90-104) years old. A total of 160 patients (71.7%) had complete stone removal (C group), while 63 patients (28.3%) had incomplete stone removal with plastic stent insertion (I group). The men:women ratio, age, performance status, and comorbidities did not differ significantly between the two groups. However, the proportion of patients with dementia was significantly higher in the I group than in the C group [C group: 34.4% (55/160) vs. I group: 50.8% (32/63), p=0.03].

Furthermore, the proportion of patients with naïve papillae at at the time of their first ERCP procedure was significantly higher in the I group than in the C group [C group: 87.5% (140/160) vs. I group: 96.8% (61/63), p=0.04] (Table 1).

Results of endoscopic procedures

The total number of procedures performed was 295 and 140 in the C and I groups, respectively. The median number of procedures performed was 1 (range 1-5 and 1-23 in the C and I groups, respectively). However, since the stent was replaced whenever stent occlusion occurred, 1 patient in I group therefore underwent ERCP a total of 23 times. The proportion of patients with at least 5 common bile duct stones was significantly higher in the I group than in the C group [C group: 8.1% (13/160) vs. I group: 20.6% (13/63), p<0.01]. The median diameter of the largest stone was 10 mm (range, 1-25 mm) and 13 mm (range, 1-32 mm) in the C and I groups, respectively. Patients with complete stone removal had significantly smaller stones than those with incomplete removal (p<0.01). The median procedure time was 31 minutes (range, 7-159 min) and 23 minutes (range, 6-125 min) in the C and I groups, respectively. The procedure time was significantly shorter in the I group than in the C group (p<0.01). In the C group, EST, EPBD, and EPLBD were performed in 42.4% (125/295), 9.5% (28/295), and 7.1% (21/295) of cases, respectively. Conversely, in the I group, EST was performed in 16.4% (23/140) of cases, EPBD in 3.6% (5/140), and EPLBD in 3.6% (5/140) (Table 2).

Complications

The incidence of hypoxemia was significantly higher in the I group than in the C group [C group: 3.1% (9/295) vs. I group: 7.9% (11/140), p<0.01], as was the incidence of bradycardia [C group: 1.7% (5/295) vs. I group: 7.1% (10/140), p<0.01]. In the I group, one patient had perforation during EPLBD, and another had Mallory-Weiss syndrome; both patients recovered with conservative treatment. However, the rate of PEP did not significantly differ between the two groups and was markedly low in both groups [C group: 3.1% (9/295) vs. I group: 0.7% (1/140), p=0.24] (Table 3).

Table 2.   Results of Endoscopic Procedures.

	Complete stone removal (n=160)	Incomplete stone removal (n=63)	p value
Total number of procedures, n	295	140	
Number of procedures, median (range)	1 (1-5)	1 (1-23)	0.36**
Patients with at least five stones, % (n)	8.1 (13/160)	20.6 (13/63)	<0.01*
Maximum size of stone, mm, median (range)	10 (1-25)	13 (1-32)	<0.01**
Procedure time, min, median (range)	31 (7-159)	23 (6-125)	<0.01**
Endoscopic procedure, % (n)			
EST	42.4 (125/295)	16.4 (23/140)	<0.01*
EPBD	9.5 (28/295)	3.6 (5/140)	0.05*
EPLBD	7.1 (21/295)	3.6 (5/140)	0.21*

*Fisher's exact test, **Mann-Whitney U test.

EST: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilation, EPLBD: endoscopic papillary large balloon dilation

Table 3.   Complications of Endoscopic Procedures.

		Complete stone removal (n=160)	Incomplete stone removal (n=63)	p value
Complications, % (n)				
During ERCP	Hypoxemia	3.1 (9/295)	7.9 (11/140)	<0.01*
	Hypotension	13.6 (40/295)	17.1 (24/140)	0.09*
	Bradycardia	1.7 (5/295)	7.1 (10/140)	<0.01*
	Perforation	0 (0/295)	0.9 (1/140)	NS
	Mallory-Weiss syndrome	0 (0/295)	0.9 (1/140)	NS
Post-ERCP	Pancreatitis	3.1 (9/295)	0.7 (1/140)	0.24*

*Fisher's exact test.

ERCP: endoscopic retrograde cholangiopancreatography, NS: not significant

The long-term prognosis

Over a median follow-up period of 492 days (range, 6-2,366 days) in the C group and 415 days (range, 0-2,085 days) in the I group, deaths were significantly higher in the I group than in the C group [C group: 32.5% (52/160) vs. I group: 61.9% (39/63), p<0.01]. In the C and I groups, 1 and 5 patients, respectively, died of biliary tract infection, and 51 and 34 patients, respectively, died of other diseases. In the C and I groups, the respective causes of death irrelevant to biliary tract infection were senility (20 and 13 patients), infection other than biliary tract infection (11 and 9 patients), heart or cerebrovascular diseases (6 and 5 patients), renal or hepatic failure (5 and 2 patients), cancer (3 and 0 patients), and unknown (6 and 5 patients) (Table 4).

The number of deaths described was used as a competing risk event in the DSS analysis. The Kaplan-Meier survival curves showed that the OS of the C group was significantly higher than that in the I group (Log-rank p<0.01) (Fig. 2). This was confirmed by the Cox proportional hazard model (z=-3.559; p<0.01).

Gray's test showed that the probability of an incident (death) was higher in group I compared to group C, in both cases "Other cause of death" (statistic=6.788; p<0.01) and a "Biliary cause of death" (statistic=7.397; p<0.01) (Fig. 3)

was higher. The latter result could be attributed to the very small number of deaths caused by biliary tract infection (n= 6).

Patients died with biliary tract infections

In this study, six patients died of biliary tract infection. One patient in the C group died of retrograde cholangitis 834 days after initial ERCP achieved complete stone removal. The other five patients in the I group died of cholangitis due to stent occulusion (Table 5).

Discussion

This multicenter retrospective study demonstrated significantly higher OS and DSS values in patients ≥90 years old who underwent complete stone removal for choledocholithiasis than in those who did not undergo complete stone removal. To our knowledge, this is the first multicenter study to evaluate the impact of complete stone removal for patients ≥90 years old in terms of the prognosis. Complete stone removal is a standard method for treating choledocholithiasis. Although patients of advanced age tend to have multiple comorbidities and functional disorders, ERCP still appears to be a safe and effective method for their treatment.

Table 4.   Causes of Death during the Follow-up Period.

	Complete stone removal (n=160)	Incomplete stone removal (n=63)	p value
Follow-up period, median, days (range)	492 (6-2366)	415 (0-2085)	0.27**
Deaths during the follow-up period, % (n)	32.5 (52/160)	61.9 (39/63)	<0.01*
Causes of death, n			
Senility	20	13	0.12*
Infection other than biliary tract infection	11	9	0.14*
Heart/cerebrovascular disease	6	5	0.34*
Renal/hepatic failure	5	2	NS
Biliary tract infection	1	5	NS
Cancer	3	0	NS
Unknown	6	5	0.34*

*Fisher's exact test, **Mann-Whitney U test.
NS: not significant
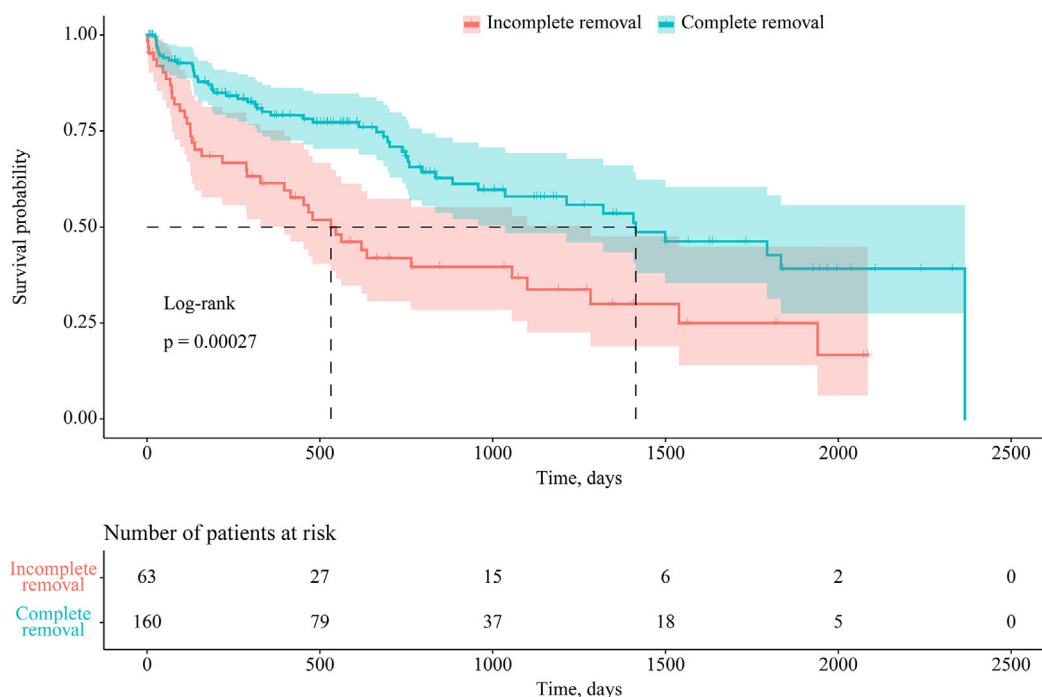
Figure 2.   Kaplan-Meier survival curves showing that the overall survival was significantly higher in the complete removal group than in the incomplete removal group.

In previous studies, the rates of technical success, complete stone removal, complications, and mortality were reportedly 80.5-100%, 86.0-98.0%, 5.0-7.9%, and 0-3.2%, respectively (15-17, 20, 21). Obana et al. reported no significant difference in the rate of complications between patients ≥80 years old and younger patients (22). Excluding the rate of complete stone removal, our results were in concordance with previous findings. Regarding complications, there was no hypoxemia, hypotension, or bradycardia resulting in the termination of ERCP. There were no serious complications related to advanced age, and these results were similar to those of previous studies (15-17, 20, 21). In particular, the incidence of PEP, which can result in patient death, was quite low in both groups [C group: 3.1% (9/295) vs. I

group: 0.7% (1/140), p=0.24]. Therefore, it was considered that therapeutic ERCP procedures for patients of advanced age (≥90 years old) could be safely performed. However, the incidences of hypoxemia and bradycardia were significantly higher in the I group than in the C group. Unfortunately, it was not possible to compare the differences in sedation due to the different medications used, and the timing of additional doses varied among institutions. However, stent placement may have been decided early in patients with vital changes due to normal sedetion, which may have led to the differences in complication rates observed between the two groups.

The rate of complete stone removal was 71.7% (160/223), which was lower than that reported in previous studies. One
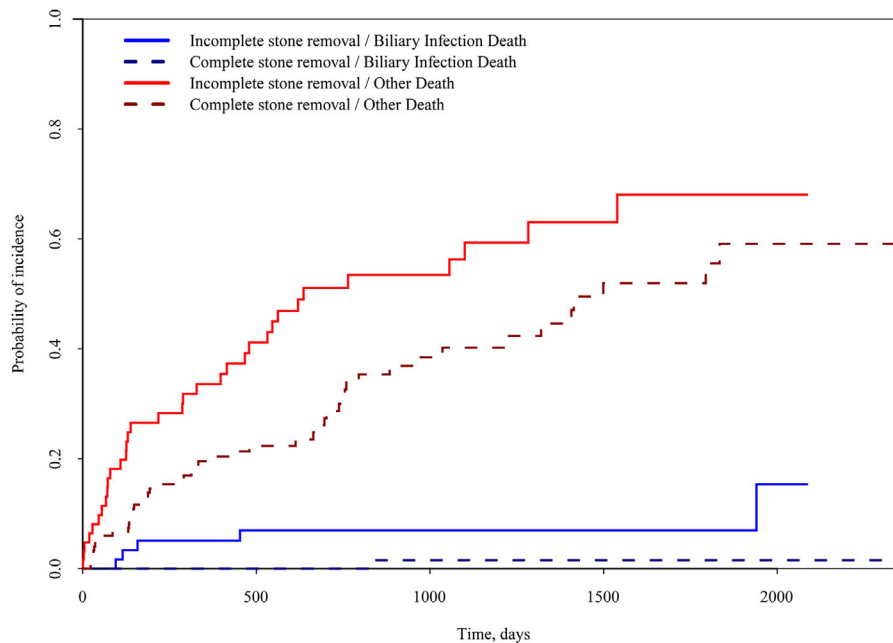
Figure 3. Gray's test showing that the probability of an incident (death) was higher in the incomplete removal group than in the complete removal group.

Table 5. Patients Died with Biliary Tract Infections.

Age at death	Sex	State of stone removal	follow-up period, days	Number of ERCPs in their life	Presence or absence of ERCP before death	Type of biliary tract infection that caused death
97	Female	Complete	834	2	Presence	Retrograde cholangitis
97	Female	Incomplete	1,940	23	Presence	Cholangitis due to stent occlusion
96	Male	Incomplete	453	3	Presence	Cholangitis due to stent occlusion
97	Female	Incomplete	158	2	Presence	Cholangitis due to stent occlusion
90	Male	Incomplete	115	2	Presence	Cholangitis due to stent occlusion
93	Female	Incomplete	95	1	Absence	Cholangitis due to stent occlusion

possible explanation for this is that the proportion of patients with dementia was significantly higher in the I group than in the C group [C group: 34.3% (55/160) vs. I group: 50.7% (32/63), p=0.03]. Dementia is not a pertinent factor for complete stone removal. However, in such cases, the treatment strategy may be decided by the attending physician and the patient's family, and whether or not treatment could result in a better prognosis may not have been clear at that time. When patients of advanced age require aggressive treatment with possible complications, if there are no data clearly demonstrating an improved survival, it is reasonable to choose a safer strategy (such as stent insertion for choledocholithiasis). In the present study, although they eventually recovered with conservative treatment, one patient who underwent EPLBD had perforation.

Furthermore, the OS rates were 67.5% (108/160) and 38.1% (24/63), and the DSS rates were 99.4% (159/160) and 92.1% (58/63) in the C and I groups, respectively, during the follow-up period. The median follow-up period for both groups was 456 days (range, 0-2,366 days). The OS in the Kaplan-Meier test and DSS in the Gray's test were sig-

nificantly higher in the C group than in the I group (p< 0.01). Therefore, even for patients of advanced age, it may be possible to improve the survival by completely removing bile duct stones. However, we cannot explain the significant difference in the OS observed between the two groups both theoretically and statistically. We speculate that the patients' comorbidities affected the OS, but there were no statistically significant differences in the evaluated comorbidities-namely coronary heart disease, respiratory disease, cerebrovascular disease, and renal failure with dialysis-between the two groups. One reason for the difference in the OS may be the lack of an evaluation of certain factors, such as activities of daily living, the body mass index, the patient's own willingness to undergo treatment, and the attending physician's willingness to prescribe treatment. Considering the aforementioned factors, patients who can be expected to have a favorable long-term prognosis may have been able to undergo aggressive complete stone removal.

A few studies have reported the mortality rate of ERCP. Sobani et al. (23) and Mitchell et al. (24) reported all-cause inpatient mortality rates of 12.2% and 13%, respectively,

while Hui et al. (25) reported a 30-day mortality rate of 7.8% in patients undergoing emergency ERCP procedures for cholangitis. In the present study, the mortality rates were 32.5% and 61.9% in the C and I groups, respectively. These rates were higher than those in previous studies, most likely because our follow-up period was longer.

In our study, the presence of dementia may have influenced the choice of treatment. For patients ≥90 years old with multiple and large bile duct stones, physicians (and possibly patients) tend to choose plastic stent insertion, which is easier and faster than complete stone removal. Although there were no significant differences in the age, performance status, or comorbidities, except for dementia, between the two groups, we did not investigate the severity of comorbidities. In addition, there might have been various factors affecting the patients' conditions that we did not consider. Regarding the DSS, Gray's test showed that the probability of an incident (death) was higher in the I group than in the C group for both "other causes of death" and "biliary cause of death." Gray's test is very sensitive; therefore, owing to the very small number of deaths from biliary tract infection (n=6), the p value for biliary tract infection should be treated very carefully. At a minimum, given the small number of deaths from biliary tract infection, the low incidence of severe complications in the C group, the eight patients in the C group who underwent subsequent complete stone removal after an aborted first attempt, and the possibility that biliary tract infections were underestimated, we can conclude that it is not necessary to avoid complete stone removal in patients due merely to advanced age.

Several limitations associated with the present study warrant mention. First, because of its retrospective nature, information on the cases excluded from therapeutic ERCP was not available. Older patients with severe comorbidities are likely at a greater risk of developing complications than young patients; furthermore, there are no established indications for endoscopic procedures in older populations. Second, the treatment strategy for choledocholithiasis in nonagenarian patients was not randomized. Although individual factors, such as the age, underlying disease, and patient preference, may have affected treatment decisions, performing a randomized trial was not possible for ethical reasons. Third, data regarding the long-term outcomes after therapeutic ERCP were dependent on the diagnosis by the family doctor of each patient, so the incidence of biliary tract infection as a long-term outcome may have been underestimated. Fourth, although patients were followed up for a median duration of 456 days, this timing was insufficient to evaluate the occurrence of biliary tract infection or death after treatment.

In conclusion, this multicenter, comparative, retrospective study showed that the OS and DSS were significantly higher in the C group than in the I group. Gray's test is very sensitive; therefore, owing to the very small number of deaths from biliary tract infection (n=6). Therefore, the p value for the biliary tract infection should be treated very carefully.

We were therefore unable to firmly conclude that complete stone removal leads to a good prognosis in extremely elderly patients. However, we did notice a trend toward a better prognosis even in patients ≥90 years old who underwent complete stone removal for choledocholithiasis than in those who did not undergo complete stone removal. In addition, in the I group, all patients died of cholangitis due to stent occlusion. Therefore, an advanced age should not be the sole reason to forgo complete stone removal in patients with choledocholithiasis, as this procedure may contribute to a better prognosis in these patients.

References

1. WHO. The World Health Report 2003 - shaping the future (Internet). World Health Organization [Internet]. 2003 [cited 2020 Jan 20]. Available from: http://www.who.int/whr/2003/en/
2. Gliedman M, Wilk P. The present status of biliary tract surgery. Surg Ann 17: 76-100, 1985.
3. Ross SO, Forsmark CE. Pancreatic and biliary disorders in the elderly. Gastroenterol Clin North Am 30: 531-545, 2001.
4. van Erpecum KJ. Gallstone disease. Complication of bile-duct stones: acute cholangitis and pancreatitis. Best Pract Res Clin Gastroenterol 20: 1139-1152, 2006.
5. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 102: 1781-1788, 2007.
6. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 335: 909-918, 1996.
7. ASGE Standards of Practice Committee; Anderson MA, Fisher L, Jain R, et al. Complications of ERCP. Gastrointest Endosc 75: 467-473, 2012.
8. Saito H, Koga T, Sakaguchi M, et al. Safety and efficacy of endoscopic removal of common bile duct stones in elderly patients ≥90 years of age. Intern Med 58: 2125-2132, 2019.
9. Hu L, Sun X, Hao J, et al. Long-term follow-up of therapeutic ERCP in 78 patients ≥90 years old. Sci Rep 4: 4918, 2014.
10. Chopra KB, Peters RA, O'Toole PA, et al. Randomized study of endoscopic biliary endoprosthesis versus duct clearance for bile duct stones in high-risk patients. Lancet 348: 791-793, 1996.
11. Bergman JJ, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. Gastrointest Endosc 42: 195-201, 1995.
12. Pisello F, Geraci G, Volsi FL, Modica G, Sciumè C. Permanent stenting in "unextractable" common bile duct stones in high risk patients. A prospective randomized study comparing two different

stents. Langenbecks Arch Surg **393**: 857-863, 2008.

13. Tanaka H, Ito K, Seno K, et al. Clinical examination of EBD treatment for elderly patients with choledocholithiasis. The Japanese Society of Geriatric Gastroenterology **7**: 86-90, 2005 (in Japanese).

14. Okuda N, Sugimoto S, Nakamura H, et al. Is complete stone removal for choledocholithiasis always necessary in extremely elderly patients? J Gastroenterol Hepatol Open **4**: 16-21, 2019.

15. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc **37**: 383-393, 1991.

16. Tsujino T, Komatsu Y, Isayama H, et al. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. Clin Gastroenterol Hepatol **3**: 376-383, 2005.

17. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc **59**: 845-864, 2004.

18. R Developement Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria [Internet]. 2017 [cited 2020 Apr 28]. Available from: https://www.R-project.org/

19. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **48**: 452-458, 2013.

20. Sugiyama M, Atomi Y. Endoscopic sphincterotomy for bile duct stones in patients 90 years of age and older. Gastrointest Endosc **52**: 187-191, 2000.

21. Koklu S, Parlak E, Yüksel O, Sahin B. Endoscopic retrograde cholangiopancreatography in the elderly: a prospective and comparative study. Age **34**: 572-577, 2005.

22. Obana T, Fujita N, Noda Y, et al. Efficacy and safety of therapeutic ERCP for the elderly with choledocholithiasis: comparison with younger patients. Intern Med **49**: 1935-1941, 2010.

23. Sobani ZA, Yunina D, Abbasi A, et al. Endoscopic retrograde cholangiopancreatography in nonagenarian patients: is it really safe? Clin Endosc **51**: 375-380, 2017.

24. Mitchell RM, O'Connor F, Dickey W. Endoscopic retrograde cholangiopancreatography is safe and effective in patients 90 years of age and older. J Clin Gastroenterol **36**: 72-74, 2003.

25. Hui CK, Liu CL, Lai KC, et al. Outcome of emergency ERCP for acute cholangitis in patients 90 years of age and older. Aliment Pharmacol Ther **19**: 153-158, 2004.