JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12198

ORIGINAL ARTICLE

Is complete stone removal for choledocholithiasis always necessary in extremely elderly patients?

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Key words
choledocholithiasis, extremely elderly, plastic stent.

Accepted for publication 21 April 2019.

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Declaration of conflict of interest: Drs. Naoko Okuda, Shinya Sugimoto, Haruka Nakamura, Hirohisa Hisada, Taishi Temma, Yuki Hashimoto, Satoshi Hayashi, Tatsuya Ito, Mayuko Takami, Jun Oyamada, and Akira Kamei declare that they have no conflicts of interest or financial ties to disclose pertaining to this article.

Abstract

Background and Aim: Endoscopic stone removal has some complications. Although the life expectancy of elderly patients has increased dramatically worldwide, little information is available on the necessity of complete endoscopic stone removal in extremely elderly patients. This study aimed to evaluate the safety and efficacy of complete endoscopic stone removal in extremely elderly patients.

Methods: All extremely elderly patients (>90 years) who underwent endoscopic stone removal for choledocholithiasis at our hospital between January 2012 and January 2017 were retrospectively evaluated. The included patients were divided into complete stone removal and incomplete stone removal groups. Complication rate, overall survival (OS), and disease-specific survival (DSS) rates were compared between the two groups.

Results: Overall, 73 patients were included in this study. The median number of stones was one (range, 0–10) and two (range, 1–12) ($P = 0.043$), while the median diameter of the largest stones was 9 (range, 0–27) and 14 (range, 5–46) mm ($P = 0.001$) in the complete and incomplete stone removal groups, respectively. During the follow-up period, OS was 60% and 39% and DSS was 95% and 97% in the complete and incomplete stone removal groups, respectively. Kaplan–Meier analysis found no significant difference in OS and DSS between the two groups ($P = 0.052$ and $P = 0.646$, respectively).

Conclusion: Complete stone removal might not always be necessary in extremely elderly patients aged ≥90 years.

Introduction

The World Health Organization Health Report has addressed the issue of global aging. It estimated a twofold increase in the number of people aged 60 years or older by 2025, reaching two billion by 2050.[1] This appraisal indicates that the proportion of elderly patients undergoing therapeutic endoscopic interventions will increase rapidly in the near future. Biliopancreatic diseases are more frequent in elderly patients than in younger patients.[2,3] Bile duct stones account for one-third of the cases of jaundice in elderly patients,[4] and gallstones affect almost one-third of patients older than 70 years.[5]

Endoscopic retrograde cholangiopancreatography (ERCP) is the method of choice for the treatment of bile duct stones. However, ERCP is not without risks as it has a reported adverse event rate of 5–10% and a mortality rate of 0.3–0.5%.[6–8] Moreover, these risks may be exacerbated by age, and their consequences may be more severe and protracted in elderly individuals. A study suggested that the risk of bleeding, cardiopulmonary events, and mortality was increased in very elderly people.[9] Another study found that sedation adverse events were more common in patients aged 80 years or older.[10] However, to our knowledge, no study has assessed the necessity of complete stone removal for choledocholithiasis in extremely elderly patients (patients aged 90 years or older) with respect to adverse events and prognosis. Hence, in this study, we aimed to assess the safety and necessity of complete stone removal in very elderly patients.

Methods

Study population. In this retrospective study, 73 patients aged 90 years or older who underwent ERCP for choledocholithiasis diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) at our hospital from January 2012 to January 2017 were enrolled. The included patients were divided into two groups, namely, complete stone removal group and incomplete stone removal group (failure to achieve complete stone removal and insertion of a plastic stent). Patient characteristics, sedation protocols, adverse events, and number of ERCPs

were compared between the two groups. The data were collected from medical records. The Institutional Review Board of our hospital provided ethical approval for this study.

Sedation procedures. All patients were monitored continuously for oxygen saturation and blood pressure (every 5 min), and electrocardiography was performed during ERCP. All patients received 2 L of oxygen through a nasal cannula. Patients were initially sedated with midazolam (1–3 mg) and meperidine (5–10 mg) intravenously. Additional doses of midazolam (1 mg) and meperidine (5 mg) were administered intermittently during the procedure if needed.

There was no protocol dedicated especially to older patients, but the dosage and frequency of each bolus was adjusted according to age and comorbidities. At our institution, sedation was performed by an endoscopist.

Endoscopic procedures. After confirming that the patients were adequately sedated, ERCP was performed using a side-viewing endoscope (JF-260 V, Olympus medical systems, Co. Ltd., Tokyo, Japan). After the common bile duct (CBD) was selectively imaged, the sizes 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 selected based on the operator's preference. For removal of the bile duct stones, retrieval balloon catheter or stone extraction baskets were used. Mechanical lithotripsy was performed when necessary. When stenting of the bile duct was performed, we used a 7-Fr pig tail stent (Zimmon®, Cook Ireland Ltd., Limerick, Ireland) or 7-Fr straight stent (Flexima™, Boston Scientific Japan, Tokyo, Japan).

The procedure time was defined as the amount of time required from insertion to removal of the endoscope. Stone removal was considered successful when no remaining radiolucent stones were visible on contrast-enhanced imaging after occlusion with a retrieval balloon. All ERCPs were supervised by three endoscopists (A.K., J.O., S.S.) who had performed >500 ERCPs.

Definition of complications. Complications during endoscopy were defined as ERCP and/or sedation adverse events, including the following: hypoxemia (oxygen saturation < 90%), hypotension (systolic blood pressure < 90 mmHg), and bradycardia (heart rate < 50/min). Bleeding was defined as a decrease in hemoglobin level of 2 g/dL or more compared with the baseline level and clinical evidence of bleeding. Acute pancreatitis was defined as abdominal pain with a threefold elevation in the serum amylase level. Perforation was defined as retroperitoneal or bowel wall perforation detected by any imaging technique.

Follow-up. After ERCP, a protease inhibitor and an antimicrobial agent were administered to prevent pancreatitis and infection.[11,12] All patients routinely underwent follow-up investigation with laboratory testing after ERCP. For patients with abdominal pain, the serum amylase level was measured, and an abdominal CT scan was performed if the symptoms persisted. After ERCP, 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 acute cholangitis was suspected. In such cases, laboratory test, abdominal CT, and then ERCP, if necessary, were performed.

Long-term follow-up was carried out by communication with their family doctor and outpatient notes. The follow-up period was defined from the date of ERCP to the date of the last visit to their family doctor or our outpatient clinic.

Statistical analysis. Quantitative variables are shown as median and range, and categorical variables are reported as frequencies and percentages. Differences between the two groups were determined using Fisher's exact test for categorical variables and Mann–Whitney *U* test for quantitative variables.

Overall survival (OS) and disease-specific survival (DSS) were estimated using the Kaplan–Meier method and were compared using the log-rank test. *P* values <0.05 were considered significant. All calculations were performed using PASW 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. The study population consisted of 18 men (25%) and 55 (75%) women. The median age was 92 (range, 90–100) years. Forty (55%) patients had complete stone removal, and 33 (45%) patients had incomplete stone removal. Age, performance status, and comorbidities did not differ between the two groups. Body mass index (BMI) was significantly larger in the complete stone removal group ($P = 0.039$) (Table 1).

All patients reported symptoms such as abdominal pain, vomiting, loss of appetite, fever, and disturbance of consciousness.

Results of endoscopic procedure. The median number of stones was one (range 0–10) and two (range 1–12) in the complete and incomplete stone removal groups, respectively. Patients in the complete stone removal had significantly fewer stones ($P = 0.043$). The median diameter of the largest stones was 9 (range, 0–27) and 14 (range, 5–46) mm in the complete and incomplete stone removal groups, respectively. Patients with complete stone removal had significantly smaller stones ($P = 0.001$). The median procedure time was 32 (range, 10–99) and 28 (range, 13–108) min in the complete and incomplete stone removal groups, respectively. The procedure time did not significantly differ between the two groups.

In the complete stone removal group, EST was performed in 28 patients, EPBD in one patient, and EPLBD in 11 patients. In the incomplete stone removal group, 5 patients underwent EST, 2 patients underwent EPLBD, and 26 patients underwent only plastic stent insertion (Table 2).

Complications. The incidence of complications was 3 of 40 (8%) in the complete stone removal group and 5 of 33 (15%) in the incomplete stone removal group (Table 3).

One patient in the complete stone removal group developed hypoxemia, hypotension, and bradycardia during treatment. In addition, there was one case of hypoxemia and one case of bradycardia in the complete stone removal group. In the incomplete stone removal group, three patients had hypotension, one

Table 1 Patient characteristics

	All (n = 73)	Complete stone removal (n = 40)	Incomplete stone removal (n = 33)	P value
Gender, male/female, n (%)	18 (25)/55 (75)	15 (38)/25 (63)	3 (9)/30 (91)	0.006*
Age, years, median (range)	92 (90–100)	93 (90–100)	92 (90–97)	0.144**
BMI, median (range)	19 (12–44)	20 (15–44)	19 (12–24)	0.039**
Performance status,† median (range)	3 (0–4)	3 (0–4)	3 (0–4)	0.400**
Comorbidities, n (%)				
Coronary heart disease	10 (14)	8 (20)	2 (6)	0.101*
Respiratory disease	8 (11)	4 (10)	4 (12)	0.999*
Cerebrovascular disease	19 (26)	13 (33)	6 (18)	0.191*
Renal failure‡	0 (0)	0 (0)	0 (0)	NA
Cancer	7 (10)	2 (5)	5 (15)	0.233*
Use of antithrombotic drugs, n (%)	20 (27)	14 (35)	6 (18)	0.123*

*Fisher's exact test.
**Mann–Whitney U test.
†Eastern Cooperative Oncology Group.
‡Renal failure that needs hemodialysis.

patient had bradycardia, and one patient had post-ERCP pancreatitis with a mild clinical course. No bleeding and perforation occurred in both groups. Differences between the groups were not significant.

OS and DSS. Over a median follow-up period of 450 (range, 6–1449) days in the complete stone removal group and 467 (range, 36–1187) days in the incomplete stone removal group, 2 and 1 patients, respectively, died of acute cholangitis, and 14 and 19 patients, respectively, died of other diseases (Table 2). OS was not significantly different between the two groups ($P = 0.052$) (Fig. 1). In the complete stone removal group, the causes of death not related to choledocholithiasis were senescence (seven patients), respiratory disorders (three patients) such as pneumonia, vascular diseases (three patients), and gallbladder carcinoma (one patient). In the incomplete stone removal group, the causes of death not related to choledocholithiasis were senescence (eight patients), respiratory disorders (two patients), vascular diseases (three patients), lung cancer (three patients), and unknown (three patients).

DSS was similar between the two groups ($P = 0.646$) (Fig. 2). Two patients in the complete stone removal group died of acute cholangitis, of which one had stone recurrence that occurred 439 days after complete stone removal. ERCP was planned, but it was unsuccessful because of failure of bile duct cannulation. He was considered unfit for further interventions, and he died 11 days after the recurrence. The other patient had complete stone removal because of acute cholangitis. Her condition did improve after the procedure; hence, ERCP was performed again 5 days after the first procedure, but there was no stone in the bile duct. She died 1 day after the second procedure.

One patient in the incomplete stone removal group died of acute cholangitis. She declined ERCP for complete stone removal after she underwent plastic stent insertion. Acute cholangitis due to stent occlusion occurred 480 days after plastic stent insertion. She consented to ERCP at that time, but she died 1 day after the procedure.

No significant differences were observed in the mean number of times of ERCP between the two groups (Table 2).

Discussion

This study demonstrated no significant difference in OS and DSS between the nonagenarian patients who underwent complete stone removal and those who underwent plastic stent insertion without complete stone removal. To the best of our knowledge, this is the first study to evaluate the necessity of complete stone removal for patients aged >90 years in terms of OS and DSS.

Complete stone removal is a standard method for treating CBD stones. Although elderly patients have multiple diseases and functional disorders, ERCP appears to be a safe and effective method even in very old patients. In previous studies, the adverse event rate of ERCP was 0.0–12.0% in nonagenarians, and there was no significant difference among younger patients.[13–17] In the present study, the adverse event rate was 11% (8/73). This is similar to the findings of previous studies. However, we cannot conclude that ERCP is safe and effective in nonagenarians because the sample sizes are rather small.

In our study, OS was 60% and 39% and DSS was 95% and 97% in the complete and incomplete stone removal groups, respectively. No other study has reported long-term OS after ERCP in nonagenarian patients, although a few studies mentioned the mortality rate. Zain et al.[17] reported an all-cause inpatient mortality rate of 12.2%, and Mitchell et al.[18] reported an all-cause inpatient mortality rate of 13%. Hui et al.[14] reported a 30-day mortality of 7.8% in patients undergoing emergency ERCPs for cholangitis.

In the present study, the mortality rate was 40% and 61% in the complete and incomplete stone removal groups, respectively. These rates were higher than in previous studies because the follow-up period was longer. In the present study, the median follow-up period was 462 (range, 6–1449) days. The high mortality rate that is unrelated to ERCP may suggest that some extremely elderly patients do not need complete stone removal. If further investigations indicate good prognostic predictors for nonagenarians who have CBD stones, we may be able to select patients who do not need complete stone removal.

Although there was no significant difference between the OS rates in the two groups ($P = 0.052$), the OS rates in the

Table 2 Results of endoscopic procedure

	All (n = 73)	Complete stone removal (n = 40)	Incomplete stone removal (n = 33)	P value
No. of stones, median, n (range)	2 (0†–12)	1 (0†–10)	2 (1–12)	0.043**
Maximum size of stone, median, mm (range)	10 (0†–46)	9 (0†–27)	14 (5–46)	0.001**
Procedure time, median, min (range)	32 (10–108)	32 (10–99)	28 (13–108)	0.378**
Endoscopic procedure, n				
EST	33	28	5	0.001*
EPBD	1	1	0	0.548*
EPLBD	13	11	2	0.016*
Only plastic stent insertion	26	0	26	0.001*
Follow-up period, median, days (range)	462 (6–1449)	450 (6–1449)	467 (36–1187)	0.406**
No. of times of ERCP during follow-up period, median (range)	1 (1–8)	1 (1–4)	1 (1–8)	0.359**
Deaths during follow-up period, n (%)	36 (49)	16 (40)	20 (61)	NA
Deaths from cholangitis during follow-up period, n (%)	3 (4)	2 (5)	1 (3)	NA

*Fisher's exact test.
**Mann–Whitney U test.
†Debris counted as 0.
EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography.

Table 3 Complications of endoscopic procedure

	All (n = 73)	Complete stone removal (n = 40)	Incomplete stone removal (n = 33)	P value
During ERCP complications, n (%)				
Hypoxemia	2 (3)	2 (5)	0 (0)	0.498*
Hypotension	5 (7)	2 (5)	3 (9)	0.653*
Bradycardia	2 (3)	1 (3)	1 (3)	0.999*
Post-ERCP complications, n (%)				
Pancreatitis	1 (1)	0 (0)	1 (3)	0.452*
Bleeding	0 (0)	0 (0)	0 (0)	NA
Perforation	0 (0)	0 (0)	0 (0)	NA

*Fisher's exact test.
ERCP, endoscopic retrograde cholangiopancreatography.

incomplete stone removal group tended to be lower than that in the complete stone removal group. As there is no difference in DSS between the two groups, this point suggests that many people died of causes unrelated to choledocholithiasis in the incomplete stone removal group. One reason is the retrospective design of this study; hence, in patients with a relatively severe condition (and high risk of death), clinicians (and patients) tend to choose plastic stent insertion, which is easier and faster than complete stone removal. Although there were no significant differences in age, performance status, and comorbidities between the two groups in our study, we did not investigate the severity of comorbidities. In addition, there may be various factors affecting the patients' conditions that we did not consider. Good prognostic predictors of health status may thus be useful in deciding the appropriate treatment of bile duct stones in extremely elderly patients.

Two-thirds of patients in the incomplete stone removal group who underwent plastic stent insertion (22/33) underwent ERCP only once in our hospital. In our study, we repeated ERCP and changed the plastic stent only when cholangitis occurred. In our region, most patients are referred to our hospital when acute cholangitis occurs. Therefore, cholangitis did not occur in many patients who underwent plastic stent insertion. In the study by

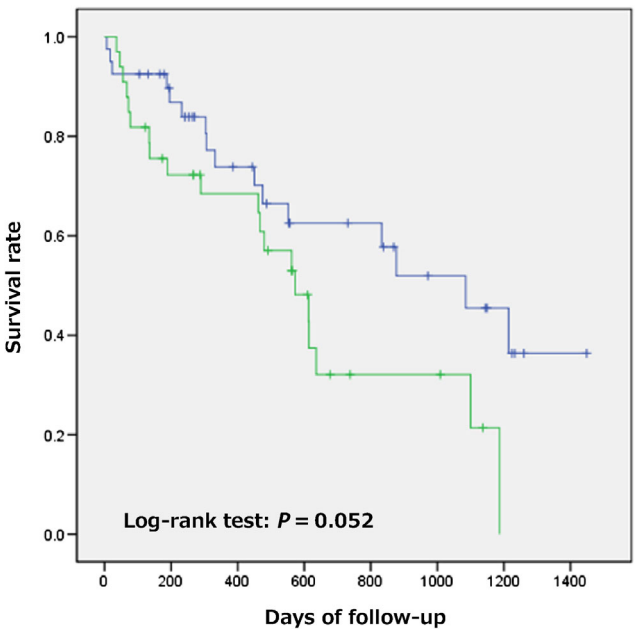

Figure 1 Kaplan–Meier curve for overall survival (OS) rate. OS was not significantly different between the two groups. ——, Complete stone removal group; ——, incomplete stone removal group

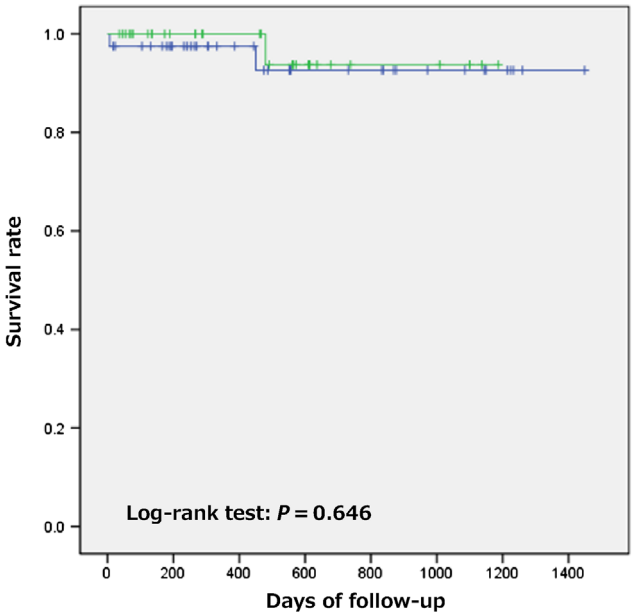

Figure 2 Kaplan–Meier curve for disease-specific survival (DSS) rate. DSS was similar between the two groups. ——, Complete stone removal group; ——, incomplete stone removal group

Giorgio et al.,[19] 39 patients underwent plastic stent insertion, and there were plans to change the plastic stent when symptoms of cholangitis occurred. Cholangitis did not occur in 25 (64.1%) patients during the follow-up period (mean, 12.8 months). One reason is that the stones decrease in size or disappear after plastic stent insertion, and cholangitis does not occur with plastic stent migration. Horiuchi et al.[20] reported that stent placement for 2 months is associated with large and/or multiple stones becoming smaller and/or disappearing. Another reason may be that the plastic stent functions as a wick and still has the potential to prevent the effects of CBD stones even with occlusion.

The fact that cholangitis did not occur with plastic stenting in many nonagenarian patients suggests that plastic stent insertion without complete stone removal is a feasible treatment of CBD stones in nonagenarian patients. However, the observation period of this study is not long enough to conclude that.

One of the strengths of this study was that it also compared the adverse event rate. There were no significant differences between complete and incomplete stone removal, although complete stone removal appeared to be more complicated and took more time than plastic stent insertion. Thus, we also suggest that complete stone removal is a good way to treat CBD stones, but it may not be always necessary if complete stone removal is difficult.

In terms of procedure time, there were also no differences between the two groups. It may be because there were two types of procedures performed in the incomplete stone removal group. In one type, we inserted a plastic stent immediately after the identification of stones in fluoroscopy without trying stone removal because the method appeared to be faster and easier. In another type, we tried complete stone removal, but because it was technically difficult, we inserted a plastic stent. In the future, if we can choose the patient who does not need complete stone removal from nonagenarian patients with choledocholithiasis, we may be able to provide a safe, shorter procedure time.

Several limitations of this study should be mentioned. First, its retrospective design introduced the potential for bias. Second, the treatment strategy for CBD stones in nonagenarian patients was not randomized. Although individual factors such as age, underlying disease, and patient preference may have affected treatment decisions, performing a randomized trial was not possible for ethical reasons. Third, although patients were observed for a median duration of 462 days, this was not sufficient to evaluate the occurrence of cholangitis after treatment.

In conclusion, this comparative, retrospective study demonstrated no significant differences in OS and DSS between the complete and incomplete stone removal groups. Moreover, it showed no significant differences in the adverse event rates between the two groups. Although complete stone removal is a safe and effective treatment for CBD stones even in nonagenarian patients, plastic stent insertion may be an acceptable option for patients when it is difficult to achieve complete stone removal or when the patient's condition is severe. Consequently, further investigation is needed for appropriate individualized treatment strategies.

Acknowledgments

We appreciate our medical assistant, Mari Shiroyama, who helped us collect data for the follow-up.

References

1 World Health Organization. *World Health Report 2003.* Available from URL: http://www.who.int/whr/2003/en/. [Cited in 20 December 2018].
2 Baron TH, Mallery JS, Hirota WK *et al*. The role of endoscopy in the evaluation and treatment of patients with pancreaticobiliary malignancy. *Gastrointest. Endosc.* 2003; **58**: 643–9.
3 Costamagna G, Shah SK, Tringali A. Current management of postoperative complications and benign biliary strictures. *Gastrointest. Endosc. Clin. N. Am.* 2003; **13**: 635–48.
4 Crocker JR. Biliary tract disease in the elderly. *Clin. Gastroenterol.* 1985; **14**: 773–809.
5 Tierney S, Lillemoe KD, Pitt HA. The current management of common duct stones. *Adv. Surg.* 1995; **28**: 271–99.
6 Andriulli A, Loperfido S, Napolitano G *et al*. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am. J. Gastroenterol.* 2007; **102**: 1781–8.
7 Freeman ML, Nelson DB, Sherman S *et al*. Complications of endoscopic biliary sphincterotomy. *N. Engl. J. Med.* 1996; **335**: 909–18.
8 Anderson MA, Fisher L, Jain R *et al*. Complications of ERCP. *Gastrointest. Endosc.* 2012; **5**: 67–473.
9 Day LW, Lin L, Somsouk M. Adverse events in older patients undergoing ERCP: a systematic review and meta-analysis. *Endosc. Int. Open*. 2014; **2**: E28–36.
10 Finkelmeier F, Tal A, Ajouaou M *et al*. ERCP in elderly patients: increased risk of sedation adverse events but low frequency of post-ERCP pancreatitis. *Gastrointest. Endosc.* 2015; **82**: 1051–9.
11 Tsujino T, Komatsu Y, Isayama H *et al*. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: A randomized, controlled trial. *Clin. Gastroenterol. Hepatol.* 2005; **3**: 376–83.

12 Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest. Endosc.* 2004; **59**: 845–64.
13 Sugiyama M, Atomi Y. Endoscopic sphincterotomy for bile duct stones in patients 90 years of age and older. *Gastrointest. Endosc.* 2000; **52**: 87–91.
14 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.* 2004; **19**: 153–8.
15 Katsinelos P, Paroutoglou G, Kountouras J, Zavos C, Beltsis A, Tzovaras G. Efficacy and safety of therapeutic ERCP in patients 90 years of age and older. *Gastrointest. Endosc.* 2006; **63**: 417–23.
16 Yun DY, Han J, Oh JS, Park KW, Shin IH, Kim HG. Is endoscopic retrograde cholangiopancreatography safe in patients 90 years of age and older? *Gut Liver*. 2014; **8**: 552–6.
17 Sobani ZA, Yunina D, Abbasi A *et al*. Endoscopic retrograde cholangiopancreatography in nonagenarian patients: is it really safe? *Clin. Endosc*. 2017; **51**: 375–80. https://doi.org/10.5946/ce.2017.123.
18 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.* 2003; **36**: 72–4.
19 Di Giorgio P, Manes G, Grimaldi E *et al*. Endoscopic plastic stenting for bile duct stones: stent changing on demand or every 3 months: A prospective comparison study. *Endoscopy*. 2013; **45**: 1014–17.
20 Horiuchi A, Nakayama Y, Kajiyama N *et al*. Biliary stenting in the management of large or multiple common bile duct stones. *Gastrointest. Endosc.* 2010; **71**: 1200–3.