patients who underwent intravenous nutrition. A recent RCT has found that the mortality rate of infected pancreatic necrosis and the incidence and mortality rates of multiple organ failure decreased in patients who underwent enteral nutrition compared in those who underwent intravenous nutrition (Level 1b) [69].

Enteral nutrition has been provided through feeding tubes inserted from the ligament of Treitz to the distal jejunum, and the infusion of nutrients into the stomach and duodenum has been avoided because of the possibility of stimulating pancreatic exocrine secretion. However, a report from Glasgow (Level 1b) [70], comparing nasogastric to nasojejunal feeding, found no difference in changes in the Acute Physiology and Chronic Health Evaluation (APACHE) II sore, C-reactive protein (CRP) level, visual analogue scale (VAS) pain score, doses of analgesic administered, or mortality rates between the two methods. A recent systematic review has shown that, in terms of safety, nasogastric feeding yielded results as good as did nasojejunal feeding in acute pancreatitis. Further accumulation of cases was considered necessary (Level 1a) [71]. Nasogastric feeding is easier to perform and it is easier to locate the tube than it is to locate a nasojejunal tube. Nasogastric nutrition should be investigated further.

An RCT [72] comparing a group of patients with acute pancreatitis in whom lactic acid bacteria was administered in addition to enteral nutrition and a group in which lactobacillus inactivated by heating was administered showed that the incidence of pancreatic infections was decreased by the addition of lactic acid bacteria (Level 2b). According to reports (Level 1b) [73–76] and a meta-analysis (Level 1a) [77] that examined the survival rate and incidence of the use of glutamine, arginine, omega-3 fatty acid and probiotics besides lactic acid bacteria in addition to enteral nutrition, no improvement was observed in the survival rate compared with a control group and no consistent results were obtained in the incidence of infectious diseases. Furthermore, an RCT (Level 1b) [78] examining the effects of administering probiotic agents enterally in patients with predicted severe acute pancreatitis reported that probiotic administration resulted, not in a decrease in the incidence of infections, but rather an increase in the mortality rate. As yet, there is no conclusion about the merits and demerits of using these agents. Further discussion is needed from now on.

CQ 7. Is regional intra-arterial infusion of protease inhibitors and antibiotics able to reduce the mortality rate and frequency of infectious pancreatic complications?

Intra-arterial local infusion of protease inhibitors and antibiotics in the early phase of the disease may lead to a decrease in the mortality rate of acute necrotizing pancreatitis and in the frequency of infectious pancreatic complications. (Recommendation C1)

The protease inhibitors used to treat acute necrotizing pancreatitis cannot easily reach the pancreas when administered intravenously and, because of ischemia [79, 80] or impaired microcirculation, they hardly penetrate into pancreatic tissue. Administration through a catheter placed in one of the arteries that supply the inflamed area of the pancreas, however, dramatically increases the tissue concentration of the protease inhibitor. A clinical study of continuous regional arterial infusion (CRAI) of a protease inhibitor and/or an antibiotic demonstrated that CRAI of nafamostat mesilate and imipenem/cilastatin was effective in reducing the mortality rate and preventing the development of pancreatic infection in acute necrotizing pancreatitis (Level 3b) [81]. A nationwide survey of CRAI therapy in acute necrotizing pancreatitis reported that severe pain disappeared in a short period of time after the initiation of CRAI of a protease inhibitor; that the frequency of infected pancreatic necrosis in the group treated with both a protease inhibitor and antibiotic via CRAI was significantly lower than that in the group treated with the protease inhibitor alone; and that the mortality rate was significantly lower in the group in which CRAI of the protease inhibitor was started within 2 days after onset than that in the group in which it was started three or more days after onset (Level 2c) [82]. A multi-center trial conducted recently in Japan using gabexate mesilate and antibiotics compared a group in which CRAI was performed with a group in which CRAI was not performed. The trial found that the duration of abdominal pain and systemic inflammatory response syndrome (SIRS) and the length of hospital stay were shortened. Also, CRP, interleukin 6 (IL6)/interleukin 10 (IL 10) ratio was found to be improved in a shorter time (Level 3b) [83].

A historical study, comparing intravenous administration and CRAI of a protease inhibitor and antibiotic, revealed a significantly higher cumulative survival rate in the CRAI group (Level 4) [84]. In a clinical study in which arterial infusion was performed after confirming, by computed tomography (CT) arteriography, that the drug had reached the site of inflammation in the pancreas, the APACHE II score and the CT severity index were improved in all subjects (Level 4) [85]. CRAI of the protease inhibitor nafamostat also prevented pancreatic necrosis in patients with severe acute pancreatitis associated with nonocclusive mesenteric ischemia (NOMI) (Level 4) [86]. Although the efficacy of CRAI of a protease inhibitor and the optimal timing is still being debated, CRAI therapy is given Recommendation C in the JPN

Guidelines. The usefulness of CRAI of a protease inhibitor should be investigated further.

CQ 8. Is blood purification therapy useful in severe acute pancreatitis?

Continuous blood purification therapy performed in the early phase of severe acute pancreatitis is likely to prevent progression to multiple organ failure. (Recommendation C1)

The activation of proinflammatory cytokines in severe acute pancreatitis is a predominant factor leading to multiple organ failure. Blood purification therapy, particularly continuous hemodiafiltration (CHDF), may inhibit the systemic inflammatory response by removing the humoral mediators. CHDF with a polymethylmethacrylate (PMMA) membrane may remove various cytokines from the bloodstream and is widely used in Japan for blood purification therapy in patients with severe acute pancreatitis complicated by multiple organ failure. A national survey of the usefulness of CHDF in severe acute pancreatitis suggested that it may prevent the progress of multiple organ failure (Level 4) [87]. It is also reported that CHDF using PMMA is useful in treating intra-abdominal hypertension (IHA) and abdominal compartment syndrome (ACS) (Level 4) [88].

However, its ability to reduce the mortality rate is still unknown.

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Therapeutic intervention and surgery of acute pancreatitis

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Abstract The clinical course of acute pancreatitis varies from mild to severe. Assessment of severity and etiology of acute pancreatitis is important to determine the strategy of management for acute pancreatitis. Acute pancreatitis is classified according to its morphology into edematous pancreatitis and necrotizing pancreatitis. Edematous pancreatitis accounts for 80–90% of acute pancreatitis and remission can be achieved in most of the patients without receiving any special treatment. Necrotizing pancreatitis occupies 10–20% of acute pancreatitis and the mortality rate is reported to be 14–25%. The mortality rate is particularly high (34–40%) for infected pancreatic necrosis that is accompanied by bacterial infection in the necrotic tissue of the pancreas (Widdison and Karanjia in Br J Surg 80:148–154, 1993; Ogawa et al. in Research of the actual situations of acute pancreatitis. Research Group for Specific Retractable Diseases, Specific Disease Measure Research Work Sponsored by Ministry of Health, Labour, and Welfare. Heisei 12 Research Report, pp 17–33, 2001). On the other hand, the mortality rate is reported to be 0–11% for sterile pancreatic necrosis which is not accompanied by bacterial infection (Ogawa et al. 2001; Bradely and

This article is based on the studies first reported in the JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.

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Allen in Am J Surg 161:19–24, 1991; Rattner et al. in Am J Surg 163:105–109, 1992). The Japanese (JPN) Guidelines were designed to provide recommendations regarding the management of acute pancreatitis in patients having a variety of clinical characteristics. This article describes the guidelines for the surgical management and interventional therapy of acute pancreatitis by incorporating the latest evidence for the management of acute pancreatitis in the Japanese-language version of JPN guidelines 2010. Eleven clinical questions (CQ) are proposed: (1) worsening clinical manifestations and hematological data, positive blood bacteria culture test, positive blood endotoxin test , and the presence of gas bubbles in and around the pancreas on CT scan are indirect findings of infected pancreatic necrosis; (2) bacteriological examination by fine needle aspiration is useful for making a definitive diagnosis of infected pancreatic necrosis; (3) conservative treatment should be performed in sterile pancreatic necrosis; (4) infected pancreatic necrosis is an indication for interventional therapy. However, conservative treatment by antibiotic administration is also available in patients who are in stable general condition; (5) early surgery for necrotizing pancreatitis is not recommended, and it should be delayed as long as possible; (6) necrosectomy is recommended as a surgical procedure for infected necrosis; (7) after necrosectomy, a long-term follow-up paying attention to pancreatic function and complications including the stricture of the bile duct and the pancreatic duct is necessary; (8) drainage including percutaneous, endoscopic and surgical procedure should be performed for pancreatic abscess; (9) if the clinical findings of pancreatic abscess are not improved by percutaneous or endoscopic drainage, surgical drainage should be performed; (10) interventional treatment should be performed for pancreatic pseudocysts that give rise to symptoms, accompany complications or increase the diameter of cysts and (11) percutaneous drainage, endoscopic drainage or surgical procedures are selected in accordance with the conditions of individual cases.

Keywords Necrotizing pancreatitis · Infected pancreatic necrosis · Sterile pancreatic necrosis · Pancreatic abscess · Pancreatic pseudocyst

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Necrotizing pancreatitis

CQ1 In which cases is infected pancreatic necrosis suspected ?

Worsening clinical manifestations and hematological data, blood bacteria culture test positive, blood endotoxin test positive, and the presence of gas bubbles in and around the pancreas on CT scan are indirect findings that lead to suspicions of infected pancreatic necrosis.

Findings of suspected infected pancreatic necrosis include worsening of clinical manifestations and hematological data, positive blood bacteria culture test , positive blood endotoxin test , and the identification of gas bubbles in and around the pancreas on CT scan, but they are findings merely suggesting the presence of infection.

CQ2 What is the most useful procedure for making a definitive diagnosis of infected pancreatic necrosis ?

Bacteriological examination by means of fine needle aspiration is useful for making a definitive diagnosis of infected pancreatic necrosis. (Recommendation A)

The method that has been established to detect infected pancreatic necrosis is bacteriological examination performed by means of CT- or US-guided local fine needle aspiration (FNA). The rate of making a correct diagnosis with this procedure is high (89–100%) (Level 2b) [5, 6]. By selecting an appropriate puncture route, the procedure can be performed safely without giving rise to complications such as intestinal injury.

On the other hand, there is a report demonstrating that the false negative rate with FNA is 20–25% [7], so it can be said that the consensus concerning the indications, timing and frequency for this procedure is not sufficient [8].

CQ3 What is the treatment policy for sterile pancreatic necrosis?

Conservative treatment should be performed as a rule in sterile pancreatic necrosis. (Recommendation B)

It is generally agreed that sterile pancreatic necrosis should be managed conservatively as a rule (Level 5) [9–11]. Many

of the patients with sterile necrosis achieve remission in response to conservative management (Level 2c–3b) [3, 8, 12, 13], although there are reports showing that surgical intervention is indicated in patients who have failed to respond to intensive conservative management (Level 2c–3b) [14–17].

CQ4 What is the treatment policy for infected pancreatic necrosis?

Infected pancreatic necrosis is an indication for interventional therapy including surgery, interventional radiology (IVR) and endoscopic treatment. (Recommendation B). However, follow-up while giving conservative treatment by means of antibiotic administration is also available in patients who are in stable general condition. (Recommendation C)

Currently, there are many reports on the treatment policy for infected pancreatic necrosis [7, 18–22]. According to Runzi et al. [19], despite prophylactic administration of antibiotics in 88 cases with necrotizing pancreatitis, 28 cases were diagnosed as having infected pancreatic necrosis, so the type of antibiotics was changed on the basis of bacteriological examination and conservative management was continued. Of these 28 cases, 12 cases underwent surgical intervention after waiting for an average of 36 days because of local infection after a diagnosis of infected pancreatic necrosis had been made and death occurred in 2 cases (16.6%). The remaining 16 cases completed conservative management by antibiotic administration (8 weeks at the longest) and death occurred in 2 cases. Also, there is a report [23] demonstrating that, of 24 cases with infected pancreatic necrosis, necrosectomy was performed in 18 cases in aggravated general condition and death occurred in 5 cases (28%), but that 6 cases in stable general condition required no surgical intervention and they all recovered with management at ICU including long-term administration of antibiotics. There is another report [24] showing that, of 31 cases with infected pancreatic necrosis, antibiotics were administered in 8 cases as the initial treatment and drainage was performed in 23 cases (percutaneous drainage in 18 cases and endoscopic drainage in 5 cases) and that 4 of these 23 cases which underwent drainage required necrosectomy due to worsening of physical condition while 8 cases which received antibiotic administration required no further treatment, of which death occurred in one of the percutaneous drainage cases and the remaining cases recovered.

Therefore, even in patients with infected pancreatic necrosis, conservative management can be the first choice of treatment on condition that their general condition is stable.

CQ5 What is the optimal timing for surgical intervention for necrotizing pancreatitis ?

Early surgery for necrotizing pancreatitis is not recommended. (Recommendation D) If surgery (necrosectomy) is performed, it should be delayed as long as possible. (Recommendation C1)

Severe acute pancreatitis often causes major organ failure in the early stage after onset, so early surgical intervention was recommended in the past when it was accompanied by signs of organ failure. However, the high mortality rate of 65% arising from early surgical intervention [1] has cast doubts on its benefits [7, 21, 22, 25–28].

A retrospective study conducted to investigate the optimal timing of surgical intervention for severe acute pancreatitis (necrotizing pancreatitis) [25] has found that the mortality rate (12%) in patients who underwent delayed surgery decreased significantly compared with that (39%) in patients who underwent early surgery. This result emphasizes the importance of delaying surgical intervention for severe acute pancreatitis as long as possible. According to the data (pancreatic resection or necrosectomy) of the only randomized controlled trial (RCT) [26] comparing early surgery (within 72 h after onset) and delayed surgery (12 days after onset), the mortality rate was 56% for early surgery and 27% for delayed surgery, respectively, and the difference was not statistically significant. However, this trial was terminated because of the very high mortality rate in patients who underwent early surgery.

A study [27] was conducted using multivariate analysis to investigate retrospectively the prognostic factors involved in surgical intervention for pancreatitis. The study compared potential factors contributing to the prognoses in 56 patients who underwent surgery (necrosectomy combined with local lavage) for necrotizing pancreatitis. Of these 56 patients, 22 patients underwent early surgery (within 12 days after onset, median: 5 days) and 34 patients underwent late surgery (after 12 days following onset, median: 20 days). According to the data of that study, the mortality rate was 54.5% for early surgery and 29.4% ($p = 0.06$) for late surgery, respectively.

Another study was conducted for 53 patients who underwent surgery for necrotizing pancreatitis to investigate retrospectively the relationship between the timing of surgery and the mortality rate. The study compared retrospectively the mortality rates in 14 patients who underwent early surgery (within 14 days following hospitalization), 11 patients who underwent intermediate surgery (15–29 days after onset), and 26 patients who underwent late surgery (waiting for 30 days after onset) and found that the mortality rate was 75% for early surgery, 45% for

intermediate surgery and 8% ($p = 0.001$) for late surgery, respectively [21]. A systematic review of 1136 cases reported in 11 references show that the earlier an operation is, the higher the mortality rate is [21].

The above findings suggest that necrosectomy for necrotizing pancreatitis should be delayed as long as possible [9, 28]. The rationale for this is that the border between normal and necrotic pancreatic tissue becomes more distinct with the passage of time, which may make it possible to minimize intraoperative hemorrhage and avoid unnecessary removal of the normal pancreas involved in necrosectomy.

CQ6 What is the optimal intervention for infected pancreatic necrosis ?

Necrosectomy is recommended as a surgical procedure for infected necrosis. (Recommendation A)

Necrosectomy with debridement of the necrotic pancreatic and peripancreatic tissue and drainage is generally agreed as a valid surgical procedure for infected pancreatic necrosis. Sufficient open necrosectomy and single-stage debridement with closed packing conducted from 1990 through 2005 yielded favorable results and the mortality rate in 167 cases of necrotizing pancreatitis (including 113 cases of infected necrosis) was 15.0% for infected pancreatitis and 4.4% for sterile pancreatitis, respectively. So, these results have become a milestone for assessing the current treatment modalities [7].

Less-invasive procedures by various approaches are currently being employed and better outcomes are reported than those achieved by conventional open surgery [29–40]. As the pancreas is a retroperitoneal organ, a combination treatment of necrosectomy by the retroperitoneal approach along with local lavage can be employed [29–31]. Also employed as a procedure using IVR is percutaneous necrosectomy, which is conducted by inserting a CT-guided drainage tube through the left abdomen to the retroperitoneum, followed by extension of fistulas and endoscopic removal of necrotic mass [32–34, 37]. There is also a report on the laparoscopic approach to the necrotic mass around the pancreas [38]. Less-invasive new treatment procedures including endoscopic transgastric necrosectomy [35, 36, 41–43] are under trial, although selection of appropriate treatment should be made considering the condition in individual cases.

CQ7 Is a long-term follow-up necessary after necrosectomy ?

Following necrosectomy, a long-term follow-up paying attention to endocrine and exocrine pancreatic function and complications including the stricture of the bile duct and the stenosis of the pancreatic duct is necessary. (Recommendation A)

Concerning the long-term prognosis of necrosectomy, there are reports indicating that necroscopy is not infrequently accompanied by decreased endocrine and exocrine pancreatic function, stricture of the bile duct and stenosis of the pancreatic duct [44–47].

According to the results of a report [47] studying the long-term prognosis of necrosectomy in 63 patients (median duration of follow-up: 28.9 months), complications occurred in 39 patients (62%) excluding pancreatic dysfunction, of which 10 patients (16%) required surgical or endoscopic treatment. Complications included 8 cases of pancreatic fistula, 4 cases of biliary tract stricture and 5 cases of pseudocysts. Also, exocrine pancreatic dysfunction occurred in 25% of cases and diabetes mellitus in 33% of cases, respectively. Furthermore, a study of 98 patients after necrosectomy [51] found that 14 patients (14.3%) developed recurrent pancreatitis caused by the stenosis of the pancreatic head and body, so they required pancreatectomy, pancreaticojejunostomy or pseudocystojejunostomy. A study [45] was conducted to investigate the endocrine and exocrine pancreatic function during the 12 months following necrosectomy in patients who survived severe gallstone-induced necrotizing pancreatitis. The patients were separated into groups: necrosectomy group (12 cases) and non-necrosectomy group (15 cases). The results show that the frequency of occurrence of steatorrhea was 25% for the former group and 0% for the latter group and the frequency of insulin replacement therapy was 33.3% for the former group and 0% for the latter group, showing that the decrease in pancreatic function was significant in the former group.

In patients who underwent necrosectomy, long-term follow-up paying attention to pancreatic duct stenosis and bile duct stricture along with other complications is required.

Pancreatic abscess

CQ8 How should pancreatic abscess be managed ?

Drainage including percutaneous, endoscopic and surgical procedure should be performed for pancreatic abscess. (Recommendation B)

Liquid puss collection is the main lesion in most patients with pancreatic abscess, so it has been reported recently that 78–86% of the patients can be cured by percutaneous drainage alone (Level 3b) [48, 49]. If a safe puncture route is assured by an imaging guidance, percutaneous drainage

may be the first choice of procedure as a radical treatment for pancreatic abscess.

CQ9 What is the indication for surgical drainage in pancreatic abscess?

If the clinical findings of pancreatic abscess are not improved by percutaneous or endoscopic drainage, surgical drainage should be performed immediately. (Recommendation B)

However, it should be noted that the favorable results reported for this treatment have all been based on retrospective studies, so some of the cases were not necessarily those of pancreatic abscess. For example, in severe cases with Ranson score of 5 or more (Level 2b) [50] and cases with multiple abscess (Level 4) [51], one-stage cure rate by percutaneous drainage is low to 30–47%.

Therefore, when signs of infection persist after drainage of the abscess, open drainage should be performed [52]. In addition to percutaneous drainage, other drainage procedures including percutaneous transgastric puncture drainage [53], endoscopic transgastric drainage [36] and endoscopic transpapillary drainage [54, 55] are also being tried, but further accumulations of cases treated by these procedures are needed.

Pancreatic pseudocysts

CQ10 What are the indications for intervention in pancreatic pseudocysts ?

Interventional treatment should be performed for pancreatic pseudocysts that give rise to symptoms, accompany complications or increase the diameter of cysts. (Recommendation A)

Indications for drainage procedures in pancreatic pseudocysts include (1) cysts accompanying symptoms such as abdominal pain, (2) those giving rise to complications such as infection and/or bleeding, (3) those increasing in size during follow-up, (4) those with a diameter of 6 cm or more, and (5) those without any tendency to decrease in size during more than 6 weeks of follow-up. Although (4) and (5) are known as "6 cm–6 week criteria", they are not absolute indications for drainage (Level 3b–4) [56, 57].

CQ11 How is interventional treatment selected for pancreatic pseudocysts?

Percutaneous drainage, endoscopic drainage or surgical procedures are selected in accordance with the conditions of individual cases including the communication with the pancreatic duct and the positional relationship between the digestive tract walls. (Recommendation A)

Treatment procedures for pancreatic pseudocysts include percutaneous drainage, endoscopic drainage, surgical drainage. There are opinions that percutaneous drainage can be an alternative procedure to surgical drainage in view of the cure rate of 80–100% that percutaneous drainage yields (Level 2c–3b) [58, 59]. However, there are also opinions that recurrence occurs in not just a few cases of pseudocysts that have temporarily resolved following percutaneous drainage (Level 3b) [60], so that surgical drainage is superior in the complete cure rate (Level 3b) [61, 62].

The only prospective controlled study (Level 2b) [50] conducted to date has found that the one-stage healing rate was 77% (20/26) for percutaneous drainage and 73% (18/26) for surgical drainage and that no differences were observed in cure and recurrence rates between the two types of drainage.

Because it has been reported that the average duration of catheterization for percutaneous drainage is 16–42 days in cases that exhibit response (Level 2c–3b) [58, 59] surgical drainage should be considered instead if no tendency to improve is observed after that duration has passed. Furthermore, percutaneous drainage has been found to be effective in cases where the morphology of the pancreatic duct is normal but does not communicate with the cysts despite the presence of pancreatic duct stenosis [63].

Endoscopic treatment including transgastric puncture, transduodenal puncture and transpapillary drainage (Level 4) is available [64–66]. Safe performance of transgastric puncture drainage was made possible using endoscopic ultrasound-guidance (Level 4) [67]. Transpapillary drainage is indicated for cases with communication between cysts and the pancreatic duct.

Surgical treatment is indicated in patients who do not respond to conservative management, percutaneous drainage or endoscopic drainage and those who are accompanied by infection and/or bleeding.

Surgical treatment is classified into fistulating operation by anastomosis between cysts and the digestive tract (cystogastrostomy and cystojejunostomy) and resection. Cases of laparoscopic surgery are reported currently [68]. External fistulating operation is selected for cases in which anastomosis is not indicated because of the immature cystic wall, and resection involving the pancreatic tail and the spleen is selected for cases in which drainage is difficult [69].

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Gallstone-induced acute pancreatitis

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Abstract In the care of acute pancreatitis, a prompt search for the etiologic condition of the disease should be conducted. A differentiation of gallstone-induced acute pancreatitis should be given top priority in its etiologic diagnosis because it is related to the decision of treatment policy. Examinations necessary for diagnosing gallstone-induced acute pancreatitis include blood tests and ultrasonography. Early ERCP/ES should be performed in patients with gallstone-induced acute pancreatitis if a complication of cholangitis and a prolonged passage disorder of the biliary tract are suspected. The treatment for bile duct stones with the use of ERCP/ES alone is not recommended in cases of gallstone-induced pancreatitis with gallbladder stones. Cholecystectomy for gallstone-induced acute pancreatitis should be performed using a laparoscopic procedure as the first option as soon as the disease has subsided.

This article is based on the studies first reported in the JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.

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Introduction

Research on the pathophysiology of acute pancreatitis has advanced dramatically during the last 20 years, and the number of randomized controlled studies (RCTs) on severe acute pancreatitis has steadily increased. The JPN guideline for the management of acute pancreatitis was published in Japanese on 2003, and in English on 2006, from the perspective of evidence-based clinical practice guidelines [1]. This paper incorporates the latest evidence, revises our guideline in relation to gallstone pancreatitis and represents the JPN Guidelines for the treatment of gallstone-induced acute pancreatitis.

Text

Chief causes of gallstone-induced pancreatitis

Gallstone-induced pancreatitis is thought to occur according to the following two mechanisms: (1) as a result of incarceration of common bile duct stones into the papilla (common pancreaticobiliary duct) followed by outflow disorders of pancreatic juice; (2) inflammation associated with cholangitis extending directly as far as the pancreas.

Diagnosis of gallstone-induced pancreatitis

CQ1 Which examinations are necessary for diagnosing gallstone-induced acute pancreatitis?

To begin with, blood tests and ultrasonography should be conducted. (Recommendation A)

A diagnosis of gallstone-induced acute pancreatitis is made when jaundice and elevated levels of ALP, γGTP and transamylase are detected by blood tests and common bile duct stones are visualized by (extracorporeal) ultrasonography (ultrasonography henceforth).

However, ultrasonography is not always able to visualize biliary stones in all cases. The ability of ultrasonography to visualize common bile duct stones decreases due to the presence of intestinal gas bubble imaging in the acute phase of pancreatitis. Common bile duct stones that induce acute pancreatitis are small sized, so visualization of the common bile duct by ultrasonography becomes difficult. Furthermore, in some cases, common bile duct stones are 'passed stones' that have already been excreted from the papilla to the duodenum. These considerations often make a diagnosis of gallstone-induced acute pancreatitis difficult. Therefore, ultrasonography should be conducted repeatedly or MRCP and EUS with higher sensitivity and specificity should be performed if ultrasonography has failed to visualize common bile duct stones, despite the presence of jaundice and elevated levels of the enzymes in the hepatobiliary system together with suspected gallstone-induced acute pancreatitis. There are cases in which ERCP is conducted on the assumption that endoscopic papillary treatment is to be provided.

Hematological examinations

There is a high possibility that gallstone-induced acute pancreatitis is present when the level of blood ALT is over 150 IU/L (48–93% for sensitivity, 34–96% for specificity, 1.4–12.0 for positive likelihood ratio and 1.8–4.9 for negative likelihood ratio) (Level 1c–2b) [2, 3], or when abnormal values were detected by blood tests in more than 3 of the items including bilirubin, ALP, γGTP, ALT, ALT/AST (85% for sensitivity, 69% for specificity, 2.7 for positive likelihood ratio, and 4.6 for negative likelihood ratio) [4]. Combination of ultrasonography and blood tests yields a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞ and negative likelihood ratio of 20.0–50.0, which enables the etiologic diagnosis of gallstone-induced acute pancreatitis (Level 2b) [4–6].

There is a report showing that blood trypsin-2-α1 antitrypsin complex/trypsinogen-1 ratio is useful in making the etiologic diagnosis of gallstone-induced acute pancreatitis because the level of blood trypsinogen increases specifically in blood trypsinogen-1 (Level 1b) [7].

Ultrasonography

As described above, in most cases, combination of ultrasonography with blood biochemical tests yields a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞ and negative likelihood ratio of 20.0–50.0, which enables the etiologic diagnosis of gallstone-induced acute pancreatitis (Level 2b) [5, 6]. Furthermore, there is a difference from report to report in the visualization rate of common bile duct stones (20–90%) by ultrasonography, so gallstone-induced pancreatitis should not be ruled out, even if ultrasonography has failed to detect biliary stones and bile duct dilatation (Level 1b–4) [8–10]. Therefore, ultrasonography should be performed repeatedly or MRCP should be conducted when gallstone-induced pancreatitis is suspected, even if the initial ultrasonography has failed to visualize biliary stones.

CT

Because CT cannot visualize biliary stones in many cases (sensitivity of 40–53%), it is not suitable for diagnosing gallstone-induced acute pancreatitis (Level 1b) [5, 10].

MRI/MRCP

Sensitivity in visualizing common bile duct stones is 20% for CT and 40% for MRCP, but is 80% for MRI/MRCP; for this reason there is an opinion that recommends MRI/MRCP as a procedure for determining indications for endoscopic papillary treatment (ERCP/ES) (Level 1b) [11]. Compared with ERCP, MRCP does not require manipulation of the papilla, so that it is able to visualize common bile duct stones in a relatively early phase of the disease because it is a minimally invasive procedure without carrying the risk of worsening the condition of acute pancreatitis.

EUS

EUS is superior to ultrasonography in terms of ability to visualize common bile duct stones (Level 1b–2b) [8, 12, 13]. In cases in which ultrasonography has failed to identify the etiology, common bile duct stones can be visualized in 59–78% of cases by performing EUS (Level 1b–3b) [12, 14, 15]. ERCP and EUS have been considered to be gold standards for making a detailed examination of biliary stones. However, the biliary tract is not able to be visualized by ERCP in some cases (14%) while detailed examinations can be carried out by EUS in all the cases that are involved (Level 1b) [16]. As mentioned above, ERCP performed at the time of an attack of acute pancreatitis is likely to further worsen inflammation.

ERCP

When jaundice and hepatic disorders are observed and the presence of common bile duct stones is strongly suspected, ERCP/ES should be performed on the assumption that endoscopic treatment of gallstone-induced pancreatitis is to be conducted. When ERCP/ES is not available, patients should be transferred to a medical facility which is in a position to perform it. There is also an opinion that recommends combined use of intraductal ultrasonography (IDUS) with ERCP on the basis of data showing that the rate of visualization of common bile duct stones is 95% for ERCP and 95% for ERCP in combination with IDUS (Level 1b) [10]. However, pancreaticography should be avoided as far as conditions permit when ERCP/EC is performed for gallstone-induced pancreatitis.

Treatment of biliary stones in gallstone-induced pancreatitis

Endoscopic treatment

CQ2 Should early ERCP+ES be performed in gallstone-induced acute pancreatitis?

Early ERCP + ES should be performed in gallstone-induced acute pancreatitis when complications of cholangitis or prolonged passage disorder of the biliary tract is suspected. (Recommendation B). Usefulness of early ERCP + ES is not supported in cases that are different from the above cases.

Of those patients in whom a diagnosis of gallstone-induced acute pancreatitis has been made or acute pancreatitis is suspected, ERCP with/without endoscopic sphincterotomy (ERCP/ES) should be performed according to the present knowledge in patients with complicated cholangitis and in patients with recurrent jaundice or its aggravation along with suspected prolongation of a passage disorder of the biliary tract. It is considered that benefits of ERCP/ES are particularly great in patients with severe acute pancreatitis. An advanced medical facility where care of acute pancreatitis is provided should always be in a position to provide ERCP/ES.

Meta-analysis

As far as an early ERCP/ES in acute pancreatitis is concerned, 4 RCTs were performed until 1997 (Level 1b) [17–20] (Table 1). Meta-analyses conducted by these RCTs (Level 1a) [21–23] reported that the incidence and mortality rates were favorable in an ERCP/ES group [21] and the incidence of complications decreased significantly only in severe cases after severity had been stratified (41.8 vs. 31.3%, $P = 0.03$) [22], a significant difference was observed in the incidence of complications (57.1 vs. 18.2% $P = 0.001$) [22] (OR = 0.27, 95% CI = 0.14–0.53) [23] and the mortality rate (17.9 vs. 3.6%, $P = 0.03$) [22].

According to the conclusions obtained by recent meta-analyses that paid attention to the sampling and end points of cases involved [24–26], early ERCP/ES decreases the incidence of complications only in severe cases but it has no effect on the mortality rate (Level 1a) [24]. In gallstone-induced acute pancreatitis without cholangitis, early ERCP/ES does not decrease the incidence of complications or the mortality rate irrespective of severity (Level 1a) [25], and irrespective of severity, early ERCP/ES decreases the incidence of local complications including infected pancreatic necrosis, pancreatic abscess and pancreatic pseudocysts (Level 1b) [26].

Table 1 Comparison of the incidence of complications and mortality rate in a group that underwent early ERCP/ES and a group that underwent conservative treatment in RCTs

Reporters	Years reported	Indications	Timing of EEI	Number of cases EEI versus ECM (severe)	Incidence of complications (%)		Mortality rate (%)	
					EEI (mild/severe)	ECM (mild/severe)	EEI (mild/severe)	ECM (mild/severe)
Neoptolemos [17]	1988	Gallstone-induced acute pancreatitis	Hospitalization <72 h	59 versus 62 (25 vs. 28)	16.9* (11.8/24.0)	33.9 (11.8/60.7)	1.7 (0/4.0)	8.1 (0/17.9)
Fan [18]	1993	Acute pancreatitis	Hospitalization <24 h	97 versus 98 (41 vs. 40)	17.5 (14.3/22.0)	28.6 (10.3/57.5)	5.2 (0/12.2)	9.2 (0/22.5)
Nowak [19]	1995	Gallstone-induced acute pancreatitis without papillary incarceration	Hospitalization <24 h	103 versus 102	16.9*	36.3	2.3*	12.8
Fölsch [20]	1997	Gallstone-induced acute pancreatitis T-Bil <5 mg/dL	Onset <72 h	126 versus 112 (26 vs. 20)	46.0	50.9	11.1	6.3
Zhou [27]	2002	Gallstone-induced acute pancreatitis	Hospitalization (<24 h)	20 versus 25 (7 vs. 7)	5.0* (0/14.3)	20.0 (0/71.4)		
Acosta [29]	2006	Gallbladder stones-related acute pancreatitis with symptoms of papillary incarceration	Onset <24–48 h	30 versus 31 (3 vs. 3)	6.7*	29.0	0	0
Oria [30]	2007	Gallstone-induced acute pancreatitis with passage disorder, without cholecystis	Onset <72 h	51 versus 51 (17 vs. 21)	21.6	17.6	5.9 (0/17.6)	2.0 (0/4.8)

EEI early endoscopic intervention (ERCP/ES), *ECM* early conservative management

* $P < 0.05$

Recent RCTs

A small RCT (Level 2b) (Table 1) [27] conducted to examine the incidence of complications, length of hospital stay and medical costs by assigning patients to either a group ($n = 20$) receiving ERCP/ES within 24 h following hospitalization and a group ($n = 25$) receiving conservative treatment found that the incidence of complications, as well as a length of hospital stay and medical costs, decreased significantly in severe cases in the ERCP/ES group.

According to an RCT (Level 2b) [28] that studied acute pancreatitis of which the causes are not limited by assigning patients either to a group that underwent EST 24 h after hospitalization or to a group that did not undergo EST, the number of days required until the disappearance of abdominal pain, the number of days for the amylase level in blood and urine tests to return to normal and the length of hospital stay were significantly shorter in the EST group. The rate of disappearance of acutely collected fluid and the rate of improvement detected by CT were also significantly superior in the EST group. However, there are no evaluations that separately confirmed the incidence and mortality rate in terms of severity.

An RCT (Level 2b) [29] (Table 1) was conducted to examine gallstone-induced acute pancreatitis accompanying papillary obstruction in terms of the incidence of complications associated with the timing of ERCP/ES. Patients with a prolonged passage disorder of the biliary tract were assigned either to a group that underwent ERCP/ES within 24–48 h after onset of the disease or to a group in which ERCP/ES was conducted when the passage disorder was found to have persisted for more than 48 h until the 48 h of observation. The results show that no death occurred in either group but that the incidence of early complications was significantly lower in the early treatment group (26 vs. 3%, $P = 0.026$) and the overall incidence of the complications was lower (29 vs. 7%, $P = 0.043$). The incidence of early and late complications was significantly higher in cases where obstruction persisted for more than 48 h, cholecystectomy was delayed and the length of hospital stay was long.

An RCT (Level 1b) [30] (Table 1) was conducted in patients who were hospitalized 48 h after onset of gallstone-induced acute pancreatitis not accompanied by cholangitis and who had, at the time of hospitalization, a bile duct diameter of $\geq$8 mm and a blood bilirubin level of $\geq$1.2 mg/dL. Patients were assigned either to a group of patients who underwent ERCP/ES within 72 h following hospitalization or to a group of patients who underwent conservative treatment. The results failed to find a significant difference in the SOFA score ($P = 0.87$), the severity detected by CT ($P = 0.88$), the incidence of localized complications (6 vs. 6%, $P = 0.99$), the overall incidence of complications (21 vs. 18%, $P = 0.80$) and the mortality rate (6 vs. 2%, $P = 1$).

From these reports, ERCP/ES is expected to be useful in cases with severe gallstone-induced acute pancreatitis accompanied by a prolonged passage disorder of the bile duct.

Alternative biliary drainage

Besides ERCP/ES, various types of procedures for biliary drainage are employed widely in Japan. At present, there is no report comparable to the above RCTs in terms of the level of quality, although there is a study that asserts the usefulness and safety of endoscopic nasobiliary drainage (ENBD) as an emergency treatment for incarcerated bile stones (Level 4) [31].

An RCT that compared the usefulness of ERCP/ES conducted within 72 h after onset of gallstone-induced severe acute pancreatitis and that of percutaneous transhepatic gallbladder drainage (Level 1b) [32] suggested that the success rate, incidence of complications and mortality rate are similar in either procedure, and that percutaneous transhepatic gallbladder drainage is useful as an alternative procedure to biliary drainage in a community in which endoscopic treatment is not available.

Safety of ERCP/ES

According to a recent national survey (Level 4) [33] investigating incidental diseases related to gastrointestinal endoscopy in Japan, the incidence of incidental diseases detected by diagnostic ERCP and therapeutic ERCP was 0.202 and 0.717%, respectively, and the mortality rate was 0.0065 and 0.052% of the overall death rate.

The safety of ERCP/ES in an acute phase of pancreatitis is asserted in a study comparing patients who underwent early ERCP/ES (within 48 h after onset of the disease) and patients who underwent elective ERCP/ES (Level 4) [34], in reports of ERCP/ES performed within 24–72 h after onset of the disease (Level 4) [35] and in a retrospective study that investigated a large number of cases in the acute phase of pancreatitis (Level 4) [36]. Also, the RCTs mentioned already in this article (Level 1b) [17–20, 27–30, 32] have found that no complications occurred that were associated with procedures and were direct causes of death and that the risk associated with ERCP/ES conducted in the early phase of pancreatitis cannot be regarded as being particularly high. Advanced medical institutions with experienced and appropriate specialists along with specialized facilities and staff are required so that they can cope with emergency ERCP/ES and bleeding that may follow. On the other hand, there is a trial that has studied the usefulness of EUS prior to ERCP/ES, in which study

ERCP/ES was conducted only when EUS indicated the presence of common bile duct stones (Level 1b) [37]. This trial is likely to contribute to a decrease in the potential risk of this procedure.

Summary

According to the present knowledge, unlimited use of early ERCP/ES is not supported. Its use should be limited to patients with symptoms such as the occurrence of jaundice or its prolongation that points to suspected passage disorder of the biliary tract and patients with a complication of cholangitis.

Surgical treatment after resolution of gallstone-induced pancreatitis

Necessity of surgical treatment

CQ3 Is selection of ES alone possible instead of cholecystectomy to prevent gallstone-induced pancreatitis with gallbladder stones?

When there is no special reason for not being able to perform cholecystectomy, ERCP + ES alone is not recommended. (Recommendation D)

Some reports have discussed the adequacy of observing the clinical course of gallstone-induced acute pancreatitis only by ERCP/ES. Some studies (Level 4) [38, 39] that reported on the observation of the clinical course of gallstone-induced acute pancreatitis conducted by using ES alone found no recurrence of pancreatitis during the 2–4 years of observation in elderly patients and patients with a high surgical risk, and claimed the usefulness of ES.

According to a prospective cohort study ($n = 117$, Level 2b) [40] of gallstone-induced acute pancreatitis, recurrent pancreatitis occurred in 2 cases of a group that underwent cholecystectomy and in one case of a group that underwent ERCP + ES alone during the 3 years of observation, and complications in the biliary system occurred in 3.6 and 11.6%, respectively, showing that the rate of occurrence was high in the ERCP + ES alone group, although the difference was not significant. Two reports (Level 4) [41, 42] that prospectively observed patients with gallstone-induced acute pancreatitis in whom ERCP + ES was performed alone found that recurrent pancreatitis occurred only in 1.5% of the patients during the 3–4 years of observation, but that some sorts of disorders of the biliary system of unknown origin occurred in 33.0%, and 12.5% of patients underwent cholecystectomy during the observation period. In both reports, many of the patients of the ERCP + ES alone group were composed of those that avoided early cholecystectomy for the reason that their surgical risk was high.

There are 3 RCTs of an ERCP + ES alone group in which indications were not limited to acute pancreatitis and a group that underwent cholecystectomy. The first report (Level 1b) [43] that concerns patients above 70 years of age (an average of 80 years) found that pancreatitis did not occur in either group during the 17 months of observation but that disorders of the biliary system occurred in 21% of the ERCP + ES alone group and 6% of the cholecystectomy group. The report concluded that cholecystectomy is desirable for elderly patients. The second RCT (Level 1b) [44] found that there was no occurrence of pancreatitis during the 2 years of observation but that there was a high rate of recurrence of symptoms associated with the biliary system in the ERCP + ES alone group (47 vs. 2%). The last report (Level 1b) [45] concerns patients above 60 years of age and shows that there was no occurrence of pancreatitis but that there was a high rate of recurrence of symptoms associated with the biliary system in the ERCP + ES alone group (24 vs. 7%).

Under these conditions, it is thought that in the absence of a special reason for not performing cholecystectomy, observation by performing ERCP + ES alone should be refrained from in cases of gallstone-induced pancreatitis, though the rate of recurrence is not said to be high.

Timing of cholecystectomy

CQ4 Which is the adequate timing for performing cholecystectomy in gallstone-induced pancreatitis?

Cholecystectomy should be performed as soon as resolution of gallstone-induced acute pancreatitis has been achieved. (Recommendation B)

Cholecystectomy has been the first option for gallstone-induced pancreatitis for the reason that cholelithiasis is one of the chief causes of acute pancreatitis. Acute pancreatitis accompanying gallstones is considered to be an indication for treatment of gallstones to prevent its recurrence. There are some opinions concerning the timing of cholecystectomy. One of them asserts that cholecystectomy should be performed as soon as the disease has occurred, while another opinion claims that it should be performed in an elective fashion while waiting for the resolution of inflammatory reaction. An RCT (Level 1b) [46] that supports early surgery found no difference in the incidence of complications (8.3 vs. 10.3%) and the mortality rate (2.8 vs. 6.9%) between the two groups on the basis of the comparison of the group that underwent early surgery within 72 h following hospitalization (early surgery group) and the group that underwent elective surgery after 3 months following hospitalization (elective surgery

group), and concluded that surgery can be performed even in the acute phase. On the other hand, an RCT (Level 1b) [47] that supports elective surgery reports, on the basis of comparison between an early surgery group that underwent surgery within 48 h following hospitalization and a delayed (elective) surgery group that underwent surgery after 48 h following hospitalization, that both the incidence of complications and the mortality rate were high (30.1 vs. 5.1% and 15.1 vs. 2.4%, respectively) in the early surgery group. However, this conclusion is unacceptable because outcomes of treatment are very poor in severe cases.

There is a recent report of a study concerning the benefit of shortening the length of hospital stay in patients who underwent laparoscopic cholecystectomy for gallstone-induced mild pancreatitis (retrospective cohort study, Level 4) [48]. The study asserts the benefit of shortening the length of hospital stay in the early surgery group (surgery is conducted according to the policy that it is to be performed if there is a tendency of improvement in abdominal tenderness and the amylase level, that is, surgery is conducted after an average of 1.8 days following hospitalization) and a benefit in the elective surgery group (surgery is conducted after the blood amylase level has returned to normal, that is, after an average of 2.8 days following hospitalization). On the other hand, there is another report (retrospective cohort study, Level 4) [49] that asserts the benefit associated with elective open laparoscopic cholecystectomy in terms of occurrence of moderate–severe complications. At present, emergency or early ECP/ES is recommended in indicated patients, so that necessity of performing surgery in the acute phase has decreased remarkably. (Refer to the previous section).

On the other hand, elective surgery has two options, that is, surgery performed during the one-time hospitalization period and surgery performed after waiting for another hospitalization after having spent sufficient time for convalescence. Pancreatitis recurs in 32–31% of patients while waiting for surgery (it occurs at the high rate within 6 weeks) (Level 4) [50–52]. In patients with gallstone-induced mild pancreatitis not accompanied by complications, search for the biliary tract and cholecystectomy should be conducted as soon as resolution of pancreatitis has been achieved even if the disease is severe.

Techniques of cholecystectomy and procedures for searching for the biliary tract

CQ5 Which operative techniques should be used for cholecystectomy after resolution of gallstone-induced pancreatitis has been achieved?

Laparoscopic cholecystectomy is the first option. (Recommendation B)

Laparoscopic surgery has been introduced actively in gallstone-induced acute pancreatitis. By totaling the data of retrospective studies conducted to date (Level 1b–4) [53–58], it was found that the rate of successful completion of laparoscopic cholecystectomy (LC) was 94.5% (79–100%), the incidence of complications was 5.5% (0–10%) and the mortality rate was 0.4% (0–2.5%) (Table 2), showing that this procedure is as successful as or more successful than open surgery.

CQ6 Which procedures are adequate for the search for the biliary tract and treatment of common bile duct stones in patients who underwent laparoscopic cholecystectomy?

According to present knowledge, selection of adequate procedures is made at the discretion of operators.

Traditionally, laparoscopic cholecystectomy (LC) and intraoperative cholangiography (IOC) plus incision of the common bile duct performed when common bile duct stones are detected have been standard procedures. However, introduction of LC has given rise to multiple options for the search for the biliary tract and treatment of common bile duct stones. The following 4 procedures are most representative. However, owing to the improvement in the diagnostic ability of MRCP, invasive search for the biliary tract such as ERCP and IOC is not always required.

1. ERCP/ES is conducted prior to surgery, while LC is performed after the diagnosis has been made and common bile duct stones have been removed.
2. Instead of ERCP, LC is performed along with IOC. When common bile duct stones are detected, LC is changed to open cholecystectomy.
3. When common bile duct stones are detected by IOC, LC is continued until its completion. ES is conducted intraoperatively or postoperatively.
4. When common bile duct stones are detected by IOC, lithotripsy through cystic-duct or with common bile duct incision is performed in a laparoscopic fashion.

There is an opinion that the LC procedure should be performed only when the presence of common bile duct stones is suspected by blood and biochemical tests or when common bile duct stones are observed (Level 1b) [58]. Furthermore, there are reports showing that the use of ERCP is likely to be adequate because the positive rate of common bile duct stones is high in the acute phase of gallstone-induced pancreatitis and the negative rate of common bile duct stones is low after remission of the disease has been achieved (Level 4) [59]. Also, the potential risk of ERCP should be taken into consideration (Level 4) [60]. An RCT (Level 1b) [58] that studied procedures and postoperative ERCP + ES for gallstone-induced acute

Table 2 Prospective cohort studies on laparoscopic cholecystectomy applied to gallstone-associated acute pancreatitis

References	Number of patients	Timing of surgery (days after the onset)	Completion rate (%)	Conversion rate (%)	Operation time (min)	Morbidity (%)	Mortality (%)	CBD exploration[d]
Rhodes et al. [53]	16	10 (4–34)[a]	100	0	50 (30–120)	0	0	15/1
Tate et al. [54]	24	7 (3–24)[a]	87.5	12.5	76 (NA)	8	0	23/0
Ballestra-Lopez et al. [55]	40	3.4/15[b,c]	100	0	86 (45–210)	10	2.5	0/40
Ricci et al. [56]	51	NA	100	0	NA	1.9	0	40/47
Uhl et al. [57]	48	10 (4–29)[a]	79	21	80 (30–225)	7.9	0	0/33
Chang et al. [58]	59	NA	100	0	NA	3.4	0	0/58

NA not assessed

[a] Median (range); [b] Mean; [c] Mild/severe disease; [d] Preoperative ERC/intra-operative cholangiogram

pancreatitis (mild to moderate severity) asserts the superiority of the LC procedure in terms of the length of hospital stay and costs. A retrospective cohort study (Level 4) [61] that examined 2 groups of patients with gallstone-induced mild pancreatitis in whom LC was performed using the technique within 2 weeks after onset and after 2 weeks following onset found favorable results in both groups. Laparoscopic treatment is very likely to become a standardized procedure along with the improvement in technical skill of operators as well as development of ideas. As for selection of procedure 2–4 when common bile duct stones have been detected by IOC, there is nothing for it but to rely on operators' skill. There is a high possibility that LC will make remarkable progress and become a standardized procedure (Level 4) [62]. Further collection of data is required concerning the safety, invasiveness, rate of successful execution and adequate selection of cases involved.

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