Introduction

This is the second of two guidelines (part IV and V) within the framework of the Guidelines on Interventional Ultrasound (INVUS) of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) describing endoscopic ultrasound (EUS)-guided therapeutic interventions. Part V deals with endoscopic ultrasound (EUS)-guided therapeutic interventions and gives recommendations for the safe and efficient performance of these advanced techniques based on the available evidence at the time of guideline preparation. It complements part IV, which addresses general aspects of interventional EUS and EUS-guided sampling [1]. The methods of guideline development are described in the introduction to the EFSUMB Guidelines on Interventional Ultrasound [2]. Levels of Evidence (LoE) and Grades of Recommendations (GoR) have been assigned according to the Oxford Centre for Evidence-based Medicine criteria (March 2009 edition) [http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009].

EUS-guided celiac plexus neurolysis/block

Background

Celiac plexus neurolysis (CPN) and celiac plexus block (CPB) are reported to offer both temporary and long-lasting pain relief, thus reducing opioid use in intra-abdominal malignancy and chronic pancreatitis [3 – 7]. Injection of bupivacaine with alcohol, phenol or triamcinolone into the celiac plexus disrupts signal transmission to the spinal cord and the central nervous system, theoretically interfering with pain perception. Several techniques have been used, including a percutaneous posterior or anterior approach.

In 1996, the first case series of endoscopic ultrasound (EUS)-guided CPN was reported [8]. The anatomical location of the celiac plexus around the origin of the celiac trunk and the superior mesenteric artery is relatively constant and is easily visualised and targeted by EUS [9].
senteric artery allows the EUS-guided technique to provide near-field, real-time visualization with a resultant potentially safer, faster and technically easier approach than percutaneous techniques. Moreover, celiac ganglia visualization by EUS in approximately 80 % of cases [9–12] allows direct injection [13].

**Technique**

Both linear and forward-view echo-endoscopes may be used for EUS-guided CPN and CPB [8, 14]. Color and power Doppler techniques allow easy identification of vascular structures (in order to avoid inadvertent intravascular injection). Combining neurolysis or block with other EUS-guided procedures reduces patient discomfort and improves cost effectiveness.

EUS-guided CPN and CPB techniques are identical. The only differences are with respect to clinical indications and the materials injected. EUS-guided CPN has been used in patients with pancreatic cancer and chronic pancreatitis by injecting bupivacaine and ethanol, while EUS-guided CPB has been used in patients with chronic pancreatitis by injecting bupivacaine with or without triamcinolone.

Briefly, the procedure is preceded by a preliminary intravenous infusion of 500–1000 cc of saline solution to prevent orthostatic hypotension. Antibiotic prophylaxis is also recommended, in particular for CPB [15]. With EUS visualization, the needle is introduced in the space between the aorta and the celiac trunk origin and flushed with 3 cc saline, followed by aspiration to ascertain inadvertent vessel penetration. Subsequently, for neurolysis, 10 ml of 0.25 % bupivacaine is injected followed by 10–20 ml of 95 %–98 % ethanol. For CPB, either bupivacaine alone or bupivacaine followed by 80 mg of triamcinolone is used. Finally, the needle is flushed with 3 cc of saline and removed [3, 16–19].

Standard aspiration needles (19 gauge (G), 22G, 25G) as well as a special 20G injection needle may be used [20]. Preliminary reports have described the effective use of phenol instead of alcohol in patients intolerant to alcohol [21] and the insertion of radioactive seeds [22, 23].

**EUS-guided celiac plexus neurolysis in patients with pancreatic and upper gastrointestinal malignancy**

**Comparison with standard analgesic treatment**

EUS-guided CPN was demonstrated to be safe and effective in alleviating refractory pain due to pancreatic cancer. 8 studies (283 patients) indicated 80 % of patients experienced pain relief [24]. A 5-study meta-analysis (119 patients) demonstrated the efficacy of EUS-guided CPN in 72.5 % of cases [25]. In a randomized controlled trial (RCT), 96 patients with advanced pancreatic cancer were randomly assigned to early EUS-guided CPN or conventional pain management, with greater pain relief observed in the early EUS-guided CPN group at three months as compared to the conventional management group [26].

A Cochrane Review compared opioids and EUS-guided CPN. EUS-guided CPN reduced pain at 4 and 8 weeks (visual analog score -0.42 and -0.44, respectively) and significantly reduced opioid consumption [4]. A meta-analysis including patients with upper gastrointestinal cancer (5 studies, n = 209) showed similar findings [5]. Overall, EUS-guided CPN is more effective than conventional pain management in patients with pancreatic and upper gastrointestinal cancer.

**Recommendation 1**

**EUS-guided CPN combined with standard analgesic treatment is superior to analgesic treatment alone in reducing pain in patients with pancreatic and upper gastrointestinal cancer** (LoE 1b, GoR B). Strong consensus (100 %)

**Single central injection vs. bilateral injections**

Results from a retrospective single-center study (n = 160, 45 % EUS-guided CPN, 55 % EUS-guided CPB) favored bilateral injections to a single central injection as the only predictor of > 50 % 7-day pain reduction [27]. Sub-group analysis in the meta-analysis of Puli et al. showed pain relief in 84 % of patients receiving bilateral injections vs. 46 % of patients receiving central injection [24]. A study of 50 patients with pancreatic cancer randomized to receive single or bilateral injections of alcohol did not observe any difference in the onset or duration of pain relief [28]. Similar findings were reported in a retrospective study with no difference between central and bilateral techniques in the median pain reduction from baseline to 4 weeks post-procedure [29]. The assumption is that there is no difference between central vs. bilateral injections in EUS-guided CPN.

**Direct celiac ganglia neurolysis**

Visualization of the ganglia is possible in approximately 80 % of patients [9–12], and when this occurs, direct injection of alcohol into the ganglia rather than random injection into the space between the aorta and the celiac trunk can be performed [13]. In a retrospective analysis of pancreatic malignancy (64 patients), direct injection of the ganglia was the best predictor of response to EUS-guided CPN. Patients with visible ganglia were >15 times more likely to respond [30]. In 34 patients with upper gastrointestinal cancer randomly assigned to either EUS-guided direct celiac ganglia neurolysis (CGN) or standard EUS-guided CPN, a higher complete response rate was observed with EUS-guided CGN (50 % vs. 18 %) [31]. In a retrospective study (41 patients), the CGN group experienced greater pain relief within 3 months after injection, a lower treatment failure rate, and faster onset and longer duration of pain relief than the CPN group [32].

**Other technical aspects**

Direct malignant invasion of the celiac ganglia and distribution of alcohol solely to the left side of the celiac trunk may preclude a positive response to EUS-guided CPN [32]. In patients with advanced abdominal cancer, a broader distribution of injected alcohol between the celiac trunk and the superior mesenteric artery (EUS-guided broad plexus neurolysis, BPN) using a 25G needle provides a better analgesic effect than standard EUS-guided CPN [33]. The injected volume of alcohol does not have an influence. In patients with pancreatic cancer, EUS-guided CPN using either 10 ml or 20 ml of absolute alcohol had similar efficacy and safety [34]. Performing EUS-guided CPN in patients with non-resectable pancreatic cancer early after diagnosis may provide better pain relief than late salvage therapy [26, 35]. There are no studies comparing percutaneous and EUS-guided CPN. A meta-analysis from 9 RCTs (5 comparing CPN with standard analgesic treatment) in patients with pancreatic and upper gastrointestinal cancer showed percutaneously guided CPN was effective in terms of pain relief and reduced opioid consumption [5].
EUS-guided celiac plexus block in patients with chronic pancreatitis

Two systematic reviews reported on the efficacy of steroid-based EUS-guided CPB in patients with refractory pain due to chronic pancreatitis (6 studies, 221 patients; 9 studies, 376 patients) showing a satisfactory reduction of abdominal pain in 52 % [25] and 60 % [24] of the patients, respectively. One of the two meta-analyses also included a group of patients treated with alcohol injection (EUS-guided CPN) [24]. Pain relief was mostly transient lasting up to 3 months [25]. The largest prospective cohort (n=90) reported the proportion of patients responding to EUS-guided CPB decreased from 55 % immediately after treatment to 10 % at 24 weeks [15]. A large retrospective study (n=248) showed that repeat EUS-guided CPB in patients with chronic pancreatitis is safe. Pain relief after the first procedure was observed in 76 % of patients and was significantly associated with response to subsequent sessions [36].

With suboptimal pain control obtained with EUS-guided CPB in chronic pancreatitis and documented serious infectious episodes, injection of triamcinolone during EUS-guided CPB has been questioned. To evaluate the effect of the addition of triamcinolone to bupivacaine, 40 patients were randomized to receive either bupivacaine alone or bupivacaine and triamcinolone. There was no significant difference in pain control between the two groups (14 % vs. 16 % for controls), and the trial was stopped [37], with no advantage of adding triamcinolone to bupivacaine for EUS-guided CPB. Preliminary results of an RCT reported a significant advantage of EUS-guided CPB using bupivacaine and triamcinolone vs. a sham procedure in terms of pain reduction. However, morphine use was similar between the two groups [38].

Leblanc et al. randomized 50 patients with chronic pancreatitis to receive one central or two bilateral injections of bupivacaine and triamcinolone without observing any difference in the duration of pain relief or onset of pain. 62 % of the patients responded to EUS-guided CPB, with an average of 38 days of pain relief among responders [39]. In conclusion, EUS-guided CPB is only moderately effective in pain control in patients with chronic pancreatitis, independent of combining bupivacaine and triamcinolone, and independent of the use of either the central or bilateral injection technique. Repeat procedures in the same patients seem to be safe and may prolong pain relief in patients responding to a first EUS-guided CPB.

EUS-guided CPB induces moderate pain improvement compared to analgesic drugs only (LoE 1b, GoR B). Strong consensus (100 %)

An RCT comparing the safety and efficacy of EUS-guided vs. computed tomography-guided CPB in chronic pancreatitis showed that the former was significantly more effective than the latter in short-term (50 % vs. 25 % at 4 weeks) and long-term pain control (30 % vs. 12 % at the end of follow-up) [40]. Another RCT comparing EUS-guided vs. percutaneous fluoroscopy-guided CPB with bupivacaine and triamcinolone demonstrated improvement in pain scores (visual analog score) in 70 % of cases in the EUS group vs. 30 % of cases in the percutaneous group [41]. In conclusion, EUS-guided CPB provides better pain control than the percutaneous techniques.

For chronic pancreatitis, percutaneous CPB has inferior efficacy compared with EUS-guided CPB, and therefore it is not recommended for use in clinical practice (LoE 1b, GoR A). Strong consensus (100 %)

Adverse events

Adverse events related to EUS-guided CPN and CPB occur in up to 30 % of cases, most commonly diarrhea (7 %), increase in abdominal pain (2 %-4 %) and hypotension (4 %). All symptoms are usually mild (grade I-II) and self-limiting [5, 42, 43]. A review of 20 studies (1142 patients) of EUS-guided CPN or CPB described adverse events in 7 % of 481 EUS-guided CPB procedures and 21 % of 661 EUS-guided CPN interventions. Minor adverse events were observed more often after EUS-guided CPN as compared to CPB (21 % vs. 7 %) [43]. Repeat EUS-guided CPN and CPB are not associated with a higher rate of adverse events [44, 45]. Serious adverse events related to EUS-guided CPN (0.2 %) and CPB (0.6 %) are reported and include bleeding, retroperitoneal abscess (in EUS-guided CPB), abdominal ischemia, permanent paralysis and death (2 cases) [43]. The risk of serious morbidity and mortality should be weighed against expected benefits particularly in patients without underlying malignancy (e.g. chronic pancreatitis).

The safety profile of EUS-guided CPN and CPB is favorable. However, due to some serious adverse events that have been reported with EUS-guided CPN, its use in patients with benign conditions should be considered with caution (LoE 4, GoR C). Broad agreement (92 %)

Antibiotic prophylaxis should be considered before EUS-guided CPB when steroids are used (LoE 5, GoR C). Strong consensus (100 %)

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**Recommendation 2**

The injection technique (central vs. bilateral) has no significant influence on the efficacy and safety of EUS-guided CPN and CPB (LoE 1b, GoR B). Strong consensus (100 %)

**Recommendation 3**

In patients with visible ganglia, EUS-guided celiac ganglia neurolysis (CGN) should be preferred to conventional EUS-guided CPN as it provides greater pain relief (LoE 1b, GoR B). Strong consensus (100 %)

**Recommendation 4**

In patients with painful non-resectable pancreatic and upper gastrointestinal cancer, EUS-guided CPN should be considered early in the course of the disease (LoE 2b, GoR C). Strong consensus (100 %)

**Recommendation 5**

EUS-guided CPB induces moderate pain improvement compared to analgesic drugs only (LoE 2a, GoR B). Strong consensus (100 %)
EUS-guided vascular interventions

Background
EUS is a valuable tool for the diagnosis of portal hypertension [46–50]. Varices are visualized as compressible anechoic tubular structures within the submucosa of the esophagus, stomach, and intestine, with color or power Doppler signal. EUS may be useful to guide endoscopic treatment of esophageal and gastric varices by identifying peri-intestinal collaterals and perforating veins, or documenting inadequate obliteration of varices and collaterals [46, 51–53]. EUS can identify rare causes of gastrointestinal bleeding, e.g. arterial pseudoaneurysm [54–58] and Dieulafoy lesions [59].

Treatment of bleeding in patients with portal hypertension
EUS-guided management of upper gastrointestinal varices and bleeding has benefits over endoscopy by identifying perforating and/or collateral veins, thus allowing precise delivery of sclerosing agents, glue, or coils [60]. EUS-guided cyanoacrylate obliteration of perforating veins in 40 consecutive patients with gastric varices was reported. In all 13 patients with active bleeding, immediate cessation of hemorrhage was achieved, but 15% of patients needed an alternative rescue therapy due to recurrent bleeding [61]. An RCT compared standard endoscopic sclerotherapy of esophageal varices with EUS-guided sclerotherapy of collateral veins. Recurrent bleeding in the EUS group was less frequent and occurred later [62]. Comparable results have been reported in a case series [63]. A comparison of EUS-guided variceal obliteration to rubber-band ligation has not been reported. The efficacy of EUS-guided coil vs. cyanoacrylate therapy has been compared in consecutive patients with gastric varices in a non-randomized study where EUS-guided coil application required fewer endoscopies and reported fewer adverse events compared with EUS-guided cyanoacrylate injection [64]. Experience from this study and case series indicates that the EUS-guided technique is effective in reducing the amount of glue injected but does not completely eliminate the risk of glue embolization. In patients with acute bleeding, the EUS approach is problematic as the necessary skills are not widely available. Technical problems include the side viewing endoscopic optic and the relatively small working channel of the majority of echo-endoscopes [61, 64–68]. Successful treatment of severe bleeding from rectal and duodenal varices has been described in case reports [69–75].

Treatment of non-variceal bleeding
Case series and single cases report successful EUS-guided treatment of non-variceal bleeding from peptic ulcer disease, Dieulafoy lesions, and gastrointestinal tumors after unsuccessful standard endoscopic treatment. Recurrent duodenal ulcer bleeding was successfully treated with EUS-guided cyanoacrylate injection in a vessel just below the ulcer [60, 76]. Case studies report successful treatment of Dieulafoy lesions with EUS-guided sclerotherapy [59, 76, 77]. In 17 patients with ineffective or unsuitable standard treatment of non-variceal bleeding, EUS-guided hemostatic interventions had a long-term success rate of 88% [78].

Pseudoaneurysm therapy and other vascular procedures
Single reports demonstrate successful EUS-guided injection treatment with the injection of cyanoacrylate, vascular coils, absolute alcohol, or 500 IU thrombin directly into pseudoaneu-

rysms of the splenic and superior mesenteric artery where conventional therapy has failed [60, 76, 78–84]. EUS-guided vascular procedures are shown to be possible in animal experiments: EUS-guided transhepatic angiography of visceral arteries and the portal venous system [85, 86], EUS-guided embolization of the portal venous system [85–89], and EUS-guided creation of a portosystemic shunt [90].

Recommendation 9
EUS-guided treatment may be considered as a salvage therapy for variceal bleeding when standard treatment fails or is not feasible (LoE 4, GoR C). Strong consensus (100%)

Recommendation 10
EUS-guided treatment may be considered in life-threatening non-variceal gastrointestinal bleeding after failure of standard treatment (LoE 4, GoR C). Strong consensus (100%)

EUS-guided drainage of pancreatic fluid collections

Background
Pancreatic and peri-pancreatic fluid collections (PFC) develop as a consequence of acute pancreatitis and resurgences of chronic pancreatitis, pancreatobiliary endoscopic interventions, endoscopic pancreatic surgery and pancreatic trauma. According to the etiology, time interval from the precipitating event, location, and morphological features, the revised Atlanta classification categorizes PFC as acute peri-pancreatic fluid collection (APFC), pancreatic pseudocyst (PPC), acute necrotic collection (ANC) and walled-off necrotic necrosis (WOPN) (Table 1) [91]. Treatment methods include percutaneous drainage, endoscopic transpapillary drainage, endoscopic transmural drainage (± EUS

Table 1 Revised Atlanta classification (2012) of pancreatic/peri-pancreatic fluid collections [91].

<table>
<thead>
<tr>
<th>type of pancreatic or peripancreatic fluid collection</th>
<th>etiology</th>
<th>capsule</th>
<th>specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute peripancreatic fluid collection, APFC</td>
<td>≤ 4 weeks after onset of acute interstitial-edematous pancreatitis</td>
<td>–</td>
<td>homogeneous, liquid, infection +/−, no features of a pseudocyst, usually spontaneous resolution</td>
</tr>
<tr>
<td>pancreatic pseudocyst, PPC</td>
<td>&gt; 4 weeks after onset of acute interstitial-edematous pancreatitis</td>
<td>+</td>
<td>round/oval, liquid, no non-liquid contents, persistent</td>
</tr>
<tr>
<td>acute necrotic collection, ANC</td>
<td>acute necrotizing pancreatitis</td>
<td>–</td>
<td>heterogeneous, liquid and necrotic contents, usually spontaneous resolution</td>
</tr>
<tr>
<td>walled-off pancreatic necrosis, WOPN</td>
<td>&gt; 4 weeks after onset of necrotizing pancreatitis</td>
<td>+</td>
<td>heterogeneous, liquid and necrotic contents, infection +/−</td>
</tr>
</tbody>
</table>

guidance), and surgical drainage either by open or laparoscopic surgery [92 – 96].

Technical success is defined by the ability to access and drain the PFC whereas treatment success comprises clinical and radiologic improvement. Clinical success is the resolution of symptoms that prompted intervention. Treatment success is related to the type of PFC. Higher success rates are described for pseudocysts and abscesses compared to pancreatic necrosis [97, 98]. Intervention is mainly indicated for infected necrosis, less often for symptomatic sterile necrosis, and should ideally be delayed as long as possible (≥4 weeks after the onset) for better necrotic tissue demarcation and liquefaction [99, 100]. With infected pancreatic necrosis, there is a significant association between the development of organ failure, need for intensive care treatment and in-hospital mortality [91, 93, 101]. The role of EUS in the evaluation of acute pancreatitis is primarily reserved for assessing and/or confirming cholechocholithiasis with subsequent stone removal by endoscopic retrograde cholangiopancreatography (ERCP), for identifying anatomic abnormalities (pancreas divisum) or to rule out malignancy [102 – 107]. Prior to any drainage procedure, differentiation of PFC from cystic neoplasms, detection of solid debris within PFC, and the identification of visceral pseudoaneurysms and portosystemic collaterals are mandatory [108 – 112].

Treatment indications
APFC and ANC regress spontaneously in the majority of cases without intervention. The rate of regression is influenced by the size and time from diagnosis. Five studies have documented that the majority of asymptomatic pseudocysts (< 4 cm) regress spontaneously and require no treatment. In a study of 91 patients, a pseudocyst diameter ≥ 6 cm or persistence > 6 months was the only independent predictor of the need for drainage [113]. The rate of spontaneous regression is lower in chronic PFC, reported at < 10%. Other factors that make spontaneous regression unlikely include: presence of multiple cysts, location in the pancreatic, wall thickness > 1 cm, absence of communication with the Wirsung duct, proximal ductal stenosis, interruption of pancreatic duct, biliary or traumatic etiology, or an increase in size on follow-up [114]. A multicenter study reported a delayed interventional approach had a lower mortality rate, with a conservative approach being possible in 62% of acute necrotic collections [99]. Drainage is considered if collections become symptomatic or infected. Infection is more common in necrotic collections, demonstrated by air within the collection on CT imaging. In the presence of infection, the prognosis worsens considerably [101, 115 – 118]. Infected collections may be sampled by EUS-guided fine needle aspiration (EUS-FNA) to obtain microbial analysis, which guides antibiotic treatment [119, 120]. With a sterile collection, luminal or biliary extrinsic compression and persistent severe abdominal pain are indications for drainage [100, 121, 122].

Recommendation 11
The decision to drain a pancreatic fluid collection (PFC) depends on clinical symptoms, condition of the patient, change in size over time, time from onset of symptoms, and infection (LoE 2b, GoR B). Strong consensus (100%).

Recommendation 12
Before performing drainage of a suspected PFC, diagnostic characterization must be performed to avoid misdiagnosis and to guide proper management decisions. Therefore, both thorough clinical history and appropriate imaging should be performed to exclude cystic pancreatic neoplasms (LoE 2b, GoR C). Strong consensus (100%).

Recommendation 13
While asymptomatic pancreatic and/or extra-pancreatic fluid collections do not warrant intervention regardless of size, location, and/or extension, drainage should be performed in case of persistent abdominal complaints or complicated disease (LoE 4, GoR C). Strong consensus (100%).

Recommendation 14
Transmural drainage of infected pancreatic necrosis should be delayed until demarcation has been accomplished (LoE 2b; GoR B). In clinically unstable patients despite appropriate intensive care, immediate drainage is recommended (LoE 5, GoR D). Strong consensus (100%).

EUS-guided drainage technique
EUS-guided drainage is suitable for pancreatic collections abutting the gastric or duodenal wall where a transgastric or transduodenal approach is feasible. Two types of linear endoscopes are available for EUS-guided PFC drainage: i) a traditional side-viewing longitudinal echoendoscope and ii) a forward-viewing echoendoscope specifically made for interventional procedures. No difference in outcome between the echoendoscopes has been documented [123].

EUS-guided drainage in a stepwise manner begins with initial visualization of the PFC using a linear echoendoscope (Fig. 1). EUS normally allows visualization of the entire cavity with contents, assesses wall maturity, measures the collection to luminal wall distance and identifies vessels (specifically: portovenous collaterals) along the puncture tract. EUS-guided drainage is performed either by a multistep or by a one-step procedure, usually guided by fluoroscopy. The multi-step technique is most frequently performed where the fluid collection is punctured with a 19G needle or a fistulotome/cystotome [18, 124, 125]. EUS-guided PFC drainage is also feasible without fluoroscopic guidance [126, 127]. A hydrophilic guidewire is then introduced via the needle followed by tract dilatation using either a tapered dilator catheter, dilating balloon or the fistulotome/cystotome itself [18, 124, 125]. When multiple stents or a stent and a nasocystic irrigation tube are to be positioned, a double guidewire approach where two guidewires are simultaneously inserted via first puncture and penetration with the fistulotome/cystotome is reasonable [128 – 132]. With WOPN, the tract is dilated to up to 20 mm at the first endoscopy, followed, when indicated, with debridement of the intracavitary solid material by introducing a forward-viewing gastroscope across the gastric or duodenal wall into the cavity. The necrotic pancreatic tissue can be removed using a combination of balloons, snares, water jets, and baskets. All possible devitalized tissue is removed on each occasion, and placed in the stomach or duodenum. To prevent bleeding, aggressive mechanical fragmentation of necrotic tissue should be performed.
A variety of stents have been used to maintain patency of the fistulous tract between the gut lumen and the PFC: single plastic stents in combination with nasocystic drainage catheters [128, 140, 141] or double pigtail stents axially placed through a metal stent. Up to now, there is no clear evidence to suggest that expandable metal stents are superior to plastic stents or different plastic stents offer a technical advantage [124, 134, 135, 142 – 144]. Expandable metal stents have a shorter procedure time as documented in an RCT [145] and a meta-analysis [146]. PFC drainage by self-expandable metal stents improved the clinical success rate and decreased the adverse event rate compared with PFC drainage by plastic stents [138]. Novel lumen-apposing self-expandable metal stents and other dedicated stents have been developed that can be deployed in a single step for PFC drainage [136, 137, 145, 147 – 162].

**Recommendation 15**

EUS-guided transmural PFC drainage may be performed with or without fluoroscopic guidance (LoE 4, GoC R). Strong consensus (100%).

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**Follow-up:**
Clinical symptoms, laboratory inflammation parameters, transabdominal ultrasound, optionally: cross-sectional imaging, endoscopy, EUS
Pancreatic fluid collections

Outcomes of EUS-guided drainage

Pancratic fluid collections
The prevalence of PPC ranges from 6–18.5% after acute pancreatitis, and the prevalence in chronic pancreatitis is 20–40% [114]. EUS-guided treatment provides comparable efficacy to surgical drainage with a shorter hospital stay and lower cost [163]. EUS-guided treatment provides comparable efficacy to surgical drainage with a shorter hospital stay and lower costs [182]. Over the last 10 years, endoscopic drainage has become important in the treatment of PPC with a comparable efficacy to surgical drainage with lower costs and a shorter hospital stay [182]. Surgical drainage is reserved for endoscopic failures, recurrence following successful endoscopic drainage or those not meeting criteria for endoscopic or percutaneous drainage.

The clinical outcomes by EUS-guided drainage of PPC are generally inferior to PPC. The treatment success rate was 94% for sterile and infected PPC versus 63% for PPC [97, 183]. An analysis comparing the efficacy of transmural drainage alone vs. transmural drainage combined with endoscopic debridement in patients with symptomatic PPC [184] found complete resolution of PPC occurred significantly more often with endoscopic debridement compared with transmural drainage alone (88% versus 45%) [184]. Mean clinical success rates of 81% to 88% and mean recurrence rates of 7% to 11% have been reported in systematic reviews concerning an aggressive endoscopic approach using transmural drainage followed by endoscopic necrosectomy [171, 185, 186]. Combining all available non-surgical drainage techniques (trans-papillary, transmural, percutaneous) gives an overall success rate of up to 94% [173].

As the necrotic component in the collection increases, the success rate progressively decreases unless aggressive endoscopic necrosectomy or concomitant percutaneous drainage is also used, with the need for surgery being more common. A meta-analysis documented a median of 4.09 drainage procedures to be necessary for effective transmural necrosectomy of PPC [185]. A study in 43 patients with symptomatic PPC treated by endoscopic drainage [110] found the number of sessions was dependent on the size of the collection and the amount of solid debris. Patients with <10% necrotic debris (n = 6) only needed a single session of endoscopic drainage, whereas patients with 10–40% solid debris (n = 33) needed ≥2 sessions. Patients with >40% solid debris (n = 4) either needed direct endoscopic debridement or surgical necrosectomy. The extent of necrosis correlated significantly with the type of treatment received by the patient [110].

The Dutch pancreatitis study group has shown that, in necrotizing pancreatitis and secondary infection, a step-up approach consisting of percutaneous drainage followed by minimally invasive retroperitoneal necrosectomy is a better treatment strategy.
than open necrosectomy [93, 187]. New-onset multiple-organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%) [188], with these results being substantiated by other studies [93, 94, 173, 181, 187, 189–195]. EUS-guided creation of multiple transmural gateways for WOPN achieves successful response in 92% of cases [140]. Analysis of the factors impacting the results of the endoscopic treatment of WOPN found multiple transmural gateway treatment was more successful than conventional single gateway access (94% vs. 62%) [196]. The optimal strategy in WOPN is a “tailored” minimally invasive approach, based on the collection size, location and stepwise response to intervention [98, 188, 197].

**Recommendation 19**
The number of repeat endoscopic treatments depends on the clinical condition of the patient, the size of the PFC and the amount of solid debris (LoE 2b, GoR B). Strong consensus (100%)

**Recommendation 20**
Treatment of WOPN including EUS-guided and percutaneous ultrasound-guided techniques should be tailored to the general clinical condition of the patient and to the characteristics of each particular collection (LoE 1b, GoR B). Strong consensus (100%)

**Recommendation 21**
EUS-guided techniques should be used to create a long-term stable large transmural endoscopic access to WOPN and/or multiple internal gateways to facilitate aggressive irrigation, drainage and/or endoscopic debridement (LoE 2b, GoR B). Strong consensus (100%)

**Recommendation 22**
A combination of transmural EUS-guided and percutaneous image-guided approaches should be considered as an alternative to surgery in refractory cases (LoE 2b, GoR B). Strong consensus (100%)

**Timing of stent removal**
There are conflicting recommendations as to the optimal time for stent removal, ranging from a few weeks to indefinitely [172, 196, 198–200]. Early stent removal may lead to recurrence of the PFC. Removal of stents at 4 weeks following endoscopic treatment of infected PFC and WOPN resulted in an optimal success rate [172]. A prospective cohort study in 47 patients in whom EUS-guided drainage of symptomatic PPC was performed showed a low long-term recurrence rate (4.7%) after stent removal at 3 weeks, if trans-papillary stenting was performed in patients with pancreatic ductal leak. Pancreatic ductal leak or disconnection was significantly associated with PPC resolution failure at 3 weeks [201]. Results of several prospective and retrospective studies suggest long-term transmural stenting in WOPN, in particular in patients with pancreatic duct leaks or disruption. In 30 patients with disconnected pancreatic duct syndrome who underwent transmural drainage of WOPN with long-term indwelling stents (mean 20.4 months, range 3 – 38 months), 5 patients had spontaneous migration of the stents (one followed by PFC recurrence), and the remaining 25 patients had no recurrence of symptomatic PFC [199]. In a retrospective study evaluating factors impacting treatment success in the endoscopic management of WOPN in patients with WOPN and disconnected pancreatic duct, transmural stents were left in place indefinitely. PFC recurrence was significantly lower in the patients with indwelling transmural stents than in patients in whom the stents were removed (0% vs. 21%) [196]. The effect of two different schedules for stent removal was evaluated in an RCT [200]. In 15 patients, stent retrieval took place after two months, and in 13 patients stent retrieval was scheduled for 12 months post-insertion. In 5/15 patients with stent removal after two months, a recurrence was seen, while none of the 13 patients with stent removal at 12 months experienced a recurrence. Stent clogging or infection was not reported in any of the 13 patients with an extended drainage period [200].

**Recommendation 23**
To avoid infection and recurrence, transmural stents should be left in place until resolution of the collection is achieved (LoE 2b, GoR C). Strong consensus (100%)

**Adverse events**
Adverse events, most frequently bleeding (2%), perforation (1.6%), secondary infection (4%) and stent migration, range from 0 – 26% [97, 146, 202, 203]. Few procedure-related mortality cases mainly due to bleeding have been reported [1, 8, 9]. Severe bleeding events occurred following erosion of the splenic and gastroduodenal artery [183] or following rupture of a visceral pseudoaneurysm [170, 173, 204]. Vascular derangements subsequent to acute pancreatitis must be excluded before performing transmural drainage [205]. Secondary infection arises from contamination of an incompletely drained PFC, from premature stent occlusion, stent dislocation, or uneven collapse [168, 198, 206–208]. Dislocation of transmural plastic stents occurs in approximately 5% of cases [43] but was also observed with specially designed covered metal stents [137]. The risk of perforation increases when the pseudocyst wall is poorly defined or is >1 cm from the intestinal lumen. Surgery is required in up to 5 – 11% of cases, with most adverse events managed conservatively, normally by an interventional radiologist or by endoscopy [10]. Pneumothorax, air embolism [189 – 191, 209] and intra-abdominal abscess are rarely reported. In WOPN compared to PPC, procedure complexity and a serious underlying clinical condition increase the morbidity and mortality [43, 185, 210]. Varadarajulu et al. reported a significantly higher adverse event rate in cases of pancreatic necrosis (16%) compared with PPC and abscesses [7]. A meta-analysis on endoscopic transmural treatment of WOPN (8 studies, n = 288) demonstrated adverse events in 21.3% and recurrence in 10.9% of cases. Surgery was needed for non-resolving WOPN in 13% [185]. Another systematic review included 13 case series and one prospective study with 455 patients and found a procedure-related morbidity of 36% (bleeding: 18%) and an overall mortality of 6% [186]. There are limited data on who should perform minimally invasive treatment including EUS-guided drainage in patients with WOPN. A consensus report from the USA suggests that management of these patients should only be performed in high-volume
centers with specialized experience in interventional endoscopy and radiology, intensive care, and surgery [93].

**Recommendation 24**
Minimally invasive treatment of WOPN including EUS-guided transmural approaches should be performed in referral centers with experience in performing image-guided interventions, pancreaticobiliary endoscopic procedures, and surgical treatment (LoE 5, GoR D). Strong consensus (100%)

**EUS-guided drainage of non-pancreatic fluid collections**

**Background**
Normally a non-pancreatic fluid collection is managed by percutaneous or operative drainage, although EUS-guided drainage of fluid collections may be as safe and effective [211]. A systematic review of EUS-guided fluid drainage procedures of collections bordering the gastrointestinal tract (mediastinum, perihepatic (subphrenic), hepatic, pelvic, perirectal space) reported technical and clinical success rates of 99% and 92%, respectively, with an overall adverse event rate of 13% [171]. Initial studies used either plastic stents or catheters. More recently, also self-expandable metallic stents have been used for abscess drainage [171].

**Technique**
The technique does not differ from EUS-guided PFC drainage. Mediastinal abscesses along with abdominal abscesses (hepatic, perihepatic, subphrenic and splenic) [216 – 223] can be drained by EUS guidance with either plastic or self-expandable metal stents [212 – 215]. Metallic stents may be preferred due to the decreased risk of leakage or occlusion [223]. Pelvic and prostatic collections may also be drained by EUS guidance, as an alternative to surgery or percutaneous techniques, with a reported technical success of 100%, a clinical success rate of 96% and low adverse events [224 – 234]. Drainage routes can be transesophageal, transgastric or transcolonic (transrectal), depending on the relationship between the collection and gastrointestinal tract [235]. Other fluid collections, e.g. bilomas, hematomas or inflammatory collections, can be drained completely by EUS guidance [215, 234 – 237]. The technique is particularly valuable for the management of postoperative intra-abdominal fluid collections after intended curative surgery or liver transplantation [215, 234 – 237].

**Recommendation 25**
EUS-guided drainage of mediastinal, abdominal or pelvic non-pancreatic fluid collections might be considered a feasible and safe option in referral centers with expertise in interventional EUS (LoE 4, GoR C). Strong consensus (100%)

**EUS-guided biliary and pancreatic interventions**

**EUS-guided cholangiography/drainage**

**Background**
Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice in obstructive jaundice due to any form of benign or malignant disease [238, 239]. ERCP is successful in >90% of cases, while selective trans-papillary cannulation and drainage may fail in locally advanced tumors with duodenal infiltration, high-grade biliary stricture or with altered anatomy especially from prior surgery. When ERCP is not feasible, alternative techniques are percutaneous transhepatic cholangiography and drainage (PTCD) or surgical biliary bypass [240 – 243]. PTCD is technically successful in >90% of cases, but compared with ERCP (morbidity 6.85%, mortality 0.33% [244 – 246]), has higher adverse events (9 – 33%, mortality 2%) and the disadvantage of a persistent external fistula when internal drainage fails [247 – 255]. Surgical decompression of obstructed bile ducts is associated with an even higher frequency of adverse events (9 – 44%) and procedure-related mortality (3%) [256 – 258]. Alternatively, EUS-guided bile duct interventions may be performed following ERCP failures. In 1996, the first cases of EUS-guided transduodenal cholangiopancreatography after failed ERCP to facilitate the success of a second attempted ERCP were reported and were technically successful in >70% of patients [259]. In 2001, EUS-guided biliary drainage was performed in two steps to achieve choledochoduodenostomy [260] and as a one-step technique to place plastic stents into the common bile duct or the dilated left intrahepatic duct (choledocoduodenostomy and hepaticojejunostomy/gastrostomy) [261]. Moreover, EUS-guided biliary rendezvous drainage in malignant obstructive jaundice after failed ERCP has been described [262].

EUS-guided cholangiography has also been described in benign diseases with unsuccessful ERCP (e.g. failed cannulation, duodenal diverticulum, choledochal cyst, chronic pancreatitis, postsurgical stricture) [263 – 267]. In one study of EUS-guided bile duct access and drainage procedures where 81% of patients had malignant disease (pancreatic cancer, cholangiocarcinoma, metastatic disease) as a cause of biliary obstruction and 19% of patients had benign disease (choledocholithiasis, benign papillary or bile duct stenosis, stricture of hepaticojejunostomy, pancreatitis), higher success rates were observed for malignant indications (90.2 vs. 77.3%) [267].

Common terminology for all EUS-guided diagnostic and therapeutic interventions independent of the access route into the bile ducts was introduced by a consortium of experts [268]. EUS-guided cholangiography and cholangiodrainage (ESC-D) is indicated if biliary drainage is necessary and conventional ERCP failed or is not feasible due to surgically altered anatomy of the upper gastrointestinal tract, gastric or duodenal obstruction, non-traversable obstruction of the papilla or bile duct, or the presence of anatomical variants (e.g. duodenal diverticulum) [268 – 270].

Many single-center and multicenter studies with different approaches, techniques and devices have reported technical and clinical success rates for ESC-D of 69 – 100% and 70 – 100%, respectively [171, 271 – 273].

**ESC-D vs. PTCD**
Patients with unresectable malignant biliary obstruction and failed ERCP (n = 25) were randomized to PTCD or ESC-D. In both groups, the technical and clinical success rates were 100%, with
Following stylet removal, bile is aspirated and contrast medium and manipulation in the desired direction [272, 279, 280]. The most important factor for practical guidewire maneuvering passage of a 0.035” guidewire, whereas a 22G needle allows a needle for the initial puncture of the bile duct. A 19G needle allows 3.8 mm working channel and a conventional 19G EUS-FNA needle has been described, but is limited by poor visibility and difficult papillary access are comparable with either PTCD or ERCP.

### Recommendation 26

In patients with malignant obstructive jaundice and failed ERCP, EUS-guided cholangiography drainage of the biliary tract can be considered as an alternative to percutaneous transhepatic cholangiographic and/or surgical intervention (LoE 2b GoR B). Strong consensus (100%).

### Technique

ESC-D can be performed by a variety of routes depending on the indication, obstruction level, and anatomical circumstances. Extrahepatic and intrahepatic routes may be used. Extrahepatic access to a dilated common bile duct is possible with the transducer in the duodenum. Intrahepatic access is normally possible from the stomach or in prior gastrectomy from the jejunum. Biliary drainage may be achieved transmurally along the respective biliary tract. Transhepatic cholangiography drainage can be performed by using a trans-papillary rendezvous maneuver (retrograde) [Table 2]. Depending on the individual anatomy and location of the stricture, the choice of drainage route is usually limited [278].

With a 3.8 mm working channel and a conventional 19G EUS-FNA needle for the initial puncture of the bile duct. A 19G needle allows passage of a 0.035” guidewire, whereas a 22G needle allows a 0.018” guidewire [18, 19]. The selection of the approach route is the most important factor for practical guidewire maneuvering and manipulation in the desired direction [272, 279, 280].

Following stylet removal, bile is aspirated and contrast medium is injected to obtain a cholangiogram. Saline needle flushing precedes the passage of the guidewire under EUS and fluoroscopy guidance.

In the rendezvous technique, the guidewire is manipulated into the duodenum. The needle and the echoendoscope are removed while maintaining the guidewire in place, with subsequent duodenoscope insertion along the guidewire. Either biliary cannulation is possible along the guidewire or the distal end of the guidewire is grasped with forceps or a snare and pulled out through the working channel. Finally, ERCP is performed using standard techniques [18, 19, 270, 272, 273].

If rendezvous is not feasible, antegrade or retrograde transmural drainage is achieved with the echoendoscope only. Direct access to the biliary tree with a needle knife with a removable inner needle has been described, but is limited by poor visibility and catheter instability. Most authors use a 19G needle for access, followed by insertion of a 0.035” guidewire and exchange of the needle for either dilators (6 – 7 French), a balloon catheter (4 – 6 mm), cystotomes (8.5 – 10 French) or a Will’s ring knife (5 French) in order to dilate the tract [278 – 282]. Finally, a stent is deployed in the fistula between the biliary tree and the intestines for biliary drainage. Both plastic and specially designed expandable metal stents (SEMS) have been used for ESC-D. No comparative studies exist, but the advantages of metal stents are the larger diameter, better visibility, higher flexibility, and a longer patency. If metal stents are used, partially covered stents are recommended to minimize the risk of biliary leakage. Biliary metal stents are not specifically designed for ESC-D, use is off-label and appropriate informed patient consent is necessary. Special stents and dedicated devices for EUS-guided biliary drainage techniques have been developed [281, 283 – 288].

### Technical and clinical outcomes

A case analysis review (n = 1127) reports overall mean technical and clinical success rates of 91% and 88%, respectively, for ESC-D [171]. A 19-center study reported that when ESC-D was attempted in 106 patients, the technical success rate was low (69%), which was attributed to inexperience and a steep learning curve. The technical success rate was higher for EUS-related (90%) vs.

<table>
<thead>
<tr>
<th>clinical situation</th>
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<tr>
<td><strong>extrahepatic approach</strong></td>
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<tr>
<td>papilla reached, but not cannulated</td>
<td>transluminal trans-papillary ESC rendezvous (ESC-RV)</td>
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<tr>
<td>papilla inaccessible or distal obstruction (CBD/ampulla/duodenum or BII resection/gastroenterostomy)</td>
<td>transluminal ESC choledocho-jejunostomy (ESC-G) or ducto-jejunostomy (ESC-D) as antegrade or retrograde drainage</td>
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<tr>
<td><strong>intrahepatic approach</strong></td>
<td></td>
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<tr>
<td>papilla inaccessible or obstruction in the distal part of the CBD with passage of the guidewire through the stenosis (BII resection, whipple, hepaticojejunostomy)</td>
<td>transluminal transhepatic ESC hepatico-jejunostomy (ESC-HJ) as antegrade drainage</td>
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<tr>
<td>papilla inaccessible or obstruction in the proximal part of the CBD without passage of the guidewire through the stenosis (intrahepatic obstruction or Roux-en-Y, hepatico-jejunostomy)</td>
<td>transluminal transhepatic ESC hepato-osophagostomy (ESC-HE), gastrostomy (ESC-HG) or jejunostomy (ESC-HJ) as retrograde drainage</td>
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ESC-D: EUS cholangiography and cholangio-drainage; CBD: common bile duct; BII: Billroth II.
ERCP-related steps (66%). Intra-ductal guidewire manipulation was the most restraining aspect, accounting for technical failure in 68 cases [289].

First reported in 2004 [262], other studies have described the rendezvous technique as effective in obtaining biliary cannulation [272, 289–291], with a cumulative success rate (9 studies, n = 267) of 81%, with a higher success rate for the extrahepatic over the intrahepatic route (87%, n = 160 vs. 65%, n = 62) [272]. The procedure and hospitalization time are significantly shorter for the extrahepatic compared to the intrahepatic approach, and the extrahepatic approach is associated with fewer adverse events, despite similar technical and clinical success rates [292].

Comparing the rendezvous technique (n = 13) with the direct transluminal approach (n = 20), no significant differences in the technical (94%) and clinical success rates (97.0%) or in the frequency of adverse events between the groups have been shown (15% vs. 10%) [293].

A comparison of the outcomes of the intrahepatic and the extrahepatic approach (n = 49) in distal malignant biliary obstruction and failed ERCP reported an overall success rate (technical success 96% vs. 91% and clinical success 91% vs. 77%, respectively), and an adverse event rate (20% vs. 12.5%) as similar for both methods [294]. An analysis of the long-term success of ESC-D (n = 240) reported no statistically significant difference in the overall success rate between the extrahepatic and intrahepatic approaches (84.3% vs. 90.4%), but when only malignant indications for ESC-D were considered, the intrahepatic approach was superior (success rate 94.9% vs. 83.8%) [267]. This varied from the results of another study in which patients (n = 68) underwent either transluminal extrahepatic or intrahepatic ESC-D using metal stents for malignant obstructive jaundice. Technical and clinical results did not differ. The intrahepatic approach was hampered by more adverse events compared to the extrahepatic route (31% vs. 9%). Multivariate analysis identified the transhepatic route as the only independent factor associated with procedure risk, with the study concluding that the preferred route is extrahepatic for transluminal and rendezvous stent placement, when both intra- and extrahepatic approaches are feasible [284]. Studies have found lower success rates with the intrahepatic compared with the extrahepatic approach due to a failure to pass a guidewire through the intrahepatic system and stricture [271, 278]. In a separate study 13% of intrahepatic approaches were converted to the extrahepatic access route [271]. A rarely used approach with a pooled success rate of 77% (30/39 cases) is the transhepatic access followed by an intraductal anterograde drainage or dilatation of strictures of the bile duct, papilla or biliobiliary anastomoses [278–281], which may then be combined with transluminal intrahepatic drainage procedures [282].

**Recommendation 27**

In EUS-guided biliary interventions, the access and drainage routes should be chosen depending on the indication, level of the biliary obstruction, anatomical condition of the upper gastrointestinal tract, and operator’s experience (LOE 2b, GoR B). Strong consensus (100%)
such, some authors suggest application of either double pigtail plastic stents as anchors or clips for the fixation of the stent [265, 268, 272, 299]. No stent migration in a preliminary experience (n = 27) with a hybrid metal stent specifically designed for intrahepatic transmural ESC-D was reported [286].

**Recommendation 30**

ESC-D is a technically demanding procedure with a relatively high procedural risk which should be performed only by experienced interventional endosonographers after careful consideration of alternative therapeutic modalities (LoE 2a, GoR B). Strong consensus (100 %)

**Recommendation 31**

If EUS-guided treatment fails, immediate drainage must be accomplished with an alternative technique (LoE 5, GoR C). Strong consensus (100 %)

**EUS-guided gallbladder drainage**

Transduodenal or transgastric access and drainage routes are feasible for EUS-guided gallbladder drainage using plastic or metal stents, including specifically designed lumen-apposing metal stents [300].

EUS-guided transgastric and transduodenal gallbladder drainage was first reported in 4 patients with advanced pancreaticobiliary malignancies and acute choledochitis after biliary stenting [301, 302]. This was followed by further reports of EUS-guided gallbladder drainage as an alternative to non-surgical percutaneous or trans-papillary access techniques in patients with acute choledochitis, who were poor candidates for surgery [303–309]. Pooled data reported a 98 % technical and a 99 % clinical success rate, with adverse events occurring in < 8 % [300]. Similar technical and clinical success rates, but lower pain scores, were reported for EUS-guided gallbladder drainage in prospective comparison to percutaneous gallbladder drainage [310].

**Recommendation 32**

In patients with acute choledochitis unsuitable for cholecystectomy, EUS-guided gallbladder drainage may be considered equivalent to percutaneous transhepatic gallbladder drainage (LoE 1b, GoR B). Strong consensus (100 %)

**EUS-guided pancreatography/drainage**

Endoscopic therapy is recommended in symptomatic patients with benign pancreatic obstruction due to chronic pancreatitis or post-surgical stenosis [240, 311, 312]. Retrograde pancreatic stenting is technically successful in 85–98 % of cases, with immediate clinical respite seen in 65–95 % but lower pain relief on follow-up only in 32–68 %. Stenting can be used as a bridging procedure prior to surgical intervention, as surgery is superior to endoscopic treatment [122, 311, 312]. When ERP fails or surgical intervention is not feasible, alternative techniques are required. EUS-guided pancreatography was first described in a patient with a symptomatic pancreatic duct stone after pancreaticoduodenectomy [313], followed by a few further reports describing EUS-guided access and interventions of the main pancreatic duct [171, 314].

**Technique, outcomes and adverse events**

In the rendezvous procedure, EUS is only used to obtain transmural access to the main pancreatic duct and to pass the guidewire through the minor or major papilla. With the anterograde technique, puncture of the main pancreatic duct and stent placement are performed using needles and guidewires through the echoendoscope. The reported clinical success rate is approximately 75 % (range 53–100 %) [171], with the adverse event rate reported at 19 % (abdominal pain, pancreatitis, bleeding, perforation, peripancreatic abscess and fluid collections) [314], reflecting the technical challenges of this technique in which re-interventions are often necessary [315].

**Recommendation 33**

EUS-guided pancreatography/drainage may be considered after failed ERCP in symptomatic patients with benign pancreatic duct obstruction, inaccessible papilla or disconnected pancreatic tail syndrome (LoE 4, GoR C). Strong consensus (100 %)

**Recommendation 34**

EUS-guided pancreatography/drainage should be performed only in referral centers by experienced interventional endosonographers, after multidisciplinary evaluation of alternative therapeutic strategies (LoE 5, GoR C). Strong consensus (100 %)

**EUS-guided tumor ablation therapy**

**Background**

EUS-guided tumor ablation includes ethanol and antitumor agent delivery, radiofrequency ablation (RFA), photodynamic treatment, implantation of radioactive seeds for brachytherapy and gold or silver fiducials to ‘target’ image-guided targeted radiation therapy. These therapies have been used for pancreatic cancer, pancreatic cystic lesions, pancreatic neuroendocrine tumors, and other malignant tumors.

**EUS-guided ethanol ablation**

**Cystic pancreatic lesions**

Pancreatic cystic tumors, either mucinous or non-mucinous, are often detected incidentally in asymptomatic patients undergoing imaging procedures [316]. Surgical resection is usually the treatment of choice for mucinous cystic tumors. However, EUS-guided ethanol lavage has been suggested as an alternative when patients are not fit for surgery [317]. The cyst is usually punctured with a 22G or 19G fine needle under EUS guidance, the fluid is aspirated, and ethanol is injected into the cyst and re-aspirated after 3–5 min [317]. The feasibility and safety of EUS-guided ethanol lavage for pancreatic cystic tumors was described in 25 patients, with complete cyst ablation observed in 35 [318]. A comparison (n = 42) of the change of pancreatic cyst size after EUS-guided lavage with either 80 % ethanol or saline solution demonstrated complete cyst ablation in 33 % of cases after 1 or 2

ethanol injections vs. 11% after 1 or 2 saline injections. However, histology of resected cysts (n = 4) showed complete ablation of neoplastic epithelium in only 1 patient [319]. Follow-up showed no cyst recurrence [320].

Repeated EUS-guided ethanol lavage for suspected branch-duct IPMN without morphological criteria for malignancy achieved cyst resolution in 5/13 patients after failure of the initial EUS-guided ethanol lavage [321].

EUS-guided ethanol lavage was applied in small mucinous cystic tumors of the pancreas (n = 13) not suitable for surgery with a response rate of 85% [322]. Other studies have combined ethanol lavage with injection of paclitaxel, a viscous, hydrophobic chemotherapeutic agent believed to have a prolonged effect [323]. A description of 14 patients with pancreatic cystic lesions treated with ethanol lavage and paclitaxel injection [323] confirmed the technical feasibility and good results of a larger series (n = 52) [324]. In the larger study, complete response was achieved in 29/52 patients (62%), with small cyst volume being predictive for treatment response [324]. The technique is also reported to be feasible in septated cystic lesions [325]. In a study of 22 patients with suspected benign pancreatic cysts, treatment with EUS-guided pancreatic cyst ablation with ethanol and paclitaxel was performed, followed at 3 months by repeat EUS-FNA for DNA analysis and possible repeat treatment. Complete and partial response was observed in 50% of patients (3–4 months) and 25% of patients (12 months after the second EUS-guided intervention) [326]. Post-ablation fluid analysis showed elimination of all baseline mutations in 8/19 patients, new mutations in 3 patients, and unchanged mutational status in 8 patients [326]. The plasma paclitaxel concentration after EUS-guided pancreatic cyst ablation was shown to be nearly undetectable and rarely caused systemic side-effects [327]. A meta-analysis of 7 studies (n = 152) reported complete cyst resolution in 56.2% of cases and partial cyst resolution in 23.7% of patients following EUS-guided ethano ablation [328]. Overall, the frequency of adverse events reported in these studies including hyperamylasemia, abdominal pain, acute pancreatitis, fever, and rarely portal and splenic vein thrombosis [329] was in a range between 0% [321] and 29% [327]. Abdominal pain (mean, 6.5%) and pancreatitis (mean, 3.9%) were the most frequent complications [328].

Pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors account for 1% of all pancreatic tumors, but their incidence is increasing. Although surgical enucleation or resection is the treatment of choice, EUS-guided ablation therapy using 95–98% ethanol is described in patients unfit for surgery [330–335]. Experimental studies in pigs have shown that EUS-guided injection of 2 ml of 40%–100% ethanol results in localized concentration-dependent pancreatic paranchymal necrosis of approximately 20 mm without adverse events [336, 337]. EUS-guided ethanol ablation of symptomatic sporadic insulinoma (size range 5–21 mm) was reported in 13 patients not fit for surgery. The step-wise injected volume was calibrated by extension of a hyperechoic blush within the tumor, ranging from 0.3 ml to 8 ml. Resolution of symptoms with euglycemia was achieved in all patients, with a single episode of mild procedure-associated pancreatitis and one hematoma with ulceration of the duodenal wall recorded, both with relatively high injected volumes (3.5 ml and 8 ml, respectively) [330–335]. Two neuroendocrine tumors were treated by EUS-guided injection of 40% ethanol in a patient with MEN 1 with subsequent normalization of the levels of vasoactive intestinal peptide and chromogranin A. The main adverse event was a small pancreatic necrosis, presumably caused by minimal ethanol effusion in a second injection session and managed by laparoscopic necrosectomy [338].

Successful EUS-guided ethanol injection treatment has been described also in solitary metastatic lymph nodes [339, 340], gastrointestinal stromal tumor [341], solitary hepatic metastases [342, 343], and left adrenal metastasis [344].

EUS-guided injection of anti-tumoral agents

Pilot and phase 1–2 studies report direct EUS-guided injection of several anti-tumoral agents into unresectable pancreatic tumors. These include cytoimplant, an allogeneic mixed lymphocyte culture [345], dendritic cells [346–348], TNFerade, a replication deficient adenovirus that expresses the tumor necrosis factor alpha [349–351], and Onyx-015, a selective adenovirus that preferentially replicates inside malignant cells [352]. Due to a substantial lack of efficacy despite the minimal number of adverse events encountered, these techniques have not become established in clinical practice.

Cytoimplant

A phase I trial reported on EUS-guided fine needle injection (FNI) of an allogeneic mixed lymphocyte culture (cytoimplant) in 8 patients with unresectable pancreatic cancer. The cytoimplant was generated from a co-culture of healthy donor and patient peripheral blood mononuclear cells to stimulate the release of cytokines and activation of immune effector cells. Escalating doses of cells were implanted into the pancreatic tumor by a single EUS-FNI. Two patients experienced partial response [345].

Dendritic cells

EUS-FNI in human pancreatic cancer of dendritic cells alone or in combination with gemcitabine was used in small series of patients for unresectable pancreatic cancer with promising albeit still preliminary results [346–348].

TNFerade

Injection of specific gene products with the purpose of selective replication in tumor cells has been reported in prospective studies for pancreatic cancer and esophageal cancer. TNFerade is a replication deficient adenovirus that expresses the tumor necrosis factor alpha (TNFα) controlled by EGR-1, a promoter inducible by radiation or chemotherapy. A phase I evaluation of EUS-guided intratumoral injection of TNFerade combined with chemoradiation before esophagectomy in 24 patients with locally advanced resectable esophageal cancer reported a complete response in six patient, and this multimodal treatment was associated with long-term survival. However, comparative studies are warranted [349]. Promising results with a phase I/II study of weekly EUS-guided or percutaneous injection of TNFerade (repeated for five weeks) combined with chemoradiation was reported in 50 patients with advanced pancreatic cancer [350]. The patients received 50.4 GY radiation and 5FU 200 mg/m² x2 for 5.5 weeks. 4 patients had complete or partial response, 7 patients could undergo surgery after the treatment, 6 of these had free resection margins, and 3 survived more than 3 months. Severe toxicity occurred in 3 patients. However, a subsequent RCT evaluating this protocol failed to show any advantage of the combined treatment vs. chemoradiation alone in terms of survival [351]. Gemcitabine offers modest improvement over 5-fluorouracil in patients with unresectable pancreatic cancer and in the adjuvant setting after

curative resection. Preliminary results of EUS-guided injection of gemcitabine were reported in 36 patients with unresectable pancreatic cancer [353].

**ONYX-015**

ONYX-015 is a selective adenovirus that preferentially replicates in malignant cells, leading to cell death. A Phase I/II trial of EUS-guided injection of ONYX-015 in 21 patients with pancreatic cancer failed to show tumor regression before initiation of gemcitabine, at the cost of severe adverse events in 4 patients [352].

**EUS-guided radiofrequency ablation**

RFA is used to ablate neoplastic tissue by local thermal-induced coagulative necrosis of the tumor [354]. Ablation in the pancreas is hazardous without real-time imaging and without additional cooling of adjacent tissue whilst treating the pancreatic head. For percutaneous RFA of unresectable pancreatic cancer, a systematic review of 5 pilot series (n = 158) reported feasibility, a median survival after RFA of 3–33 months, and a procedure-related morbidity and mortality of 4–37% and 0–19%, respectively [355, 356]. The results and safety of EUS-guided RFA (liver, pancreas, lymph nodes) have been evaluated only in animal experiments with encouraging results [357–361], and only in a few human patients with pancreatic tumors [362, 363]. The combination of cryotherapy and RFA has the advantage of the two technologies: the more effective cooling by cryogenic gas permits more RF-induced interstitial devitalizing effects than heat alone. Less power is needed than with conventional RFA systems to obtain the same result, resulting in less collateral damage. Under EUS guidance, the cryoablation probe, a flexible bipolar device that combines radiofrequency with cryogenic cooling, was used to treat 22 patients with unresectable stage III pancreatic adenocarcinoma with fixed RF power (heating) of 18 W and fixed pressure (cooling). Technical problems prohibited application of the probe in 27% of patients. The effect of this treatment was difficult to determine. Although severe procedure-related adverse events were not observed, only 6 patients seemed to benefit from partial tumor regression [363]. Experimental studies have been performed for EUS-guided photodynamic therapy and Nd:YAG-laser treatment [364–367].

**EUS-guided interstitial brachytherapy**

EUS guidance can also be used to implant intra-tumoral radioactive seeds. This is a safe, simple and minimally invasive technique for interstitial brachytherapy of the pancreas. However, the biological effectiveness of $^{125}$I seeds in pancreatic cancer cells has yet to be determined.

EUS-guided $^{125}$I implantation was technically feasible in 15 patients with unresectable pancreatic cancer, 8 with stage III disease and 7 with stage IV disease [368]. The clinical efficacy and safety of EUS-guided implantation of radioactive $^{125}$I seeds in advanced pancreatic cancer was evaluated with routine gemcitabine-based 5-FU chemotherapy 1 week after brachytherapy [23]. Compared with brachytherapy alone [369], the combination of chemotherapy and radioactive $^{125}$I seeds did not demonstrate better tumor response nor long-term effects. Partial tumor response and pain relief were observed in 27% and 30% of patients, respectively. Local adverse events or grade III toxicity developed in 40% of patients [369]. Radioactive metal seeds have also been applied in metastatic lymph nodes in the retroperitoneum and in the mediastinum, but with only single reported cases describing response to treatment [370].

**EUS-guided intratumoral placement of fiducial markers**

Stereotactic body radiation therapy relies on image-guided radiotherapy to allow radiation dose escalation to tumors with simultaneous sparing of surrounding normal tissue through the use of imaging to verify target delineation and treatment delivery. Fiducial markers are useful to facilitate the quantification of respiratory-associated tumor motion [371] and allow reproducible daily treatment delivery. Fiducial markers include radiopaque spheres, coils, or seeds that are implanted in or near the tumor. EUS-guided fiducial placement has been reported to be feasible and safe in several studies of inoperable pancreatic, abdominal or mediastinal malignancy [171, 372–376]. The reported success rate is between 84.6% and 100%, and adverse events are few (7/278, 2.5%) and limited to mild pancreatitis, abdominal pain and infection [171]. In inoperable pancreatic cancer or hepatic malignant lesions eligible for radiation therapy (n = 32), a 100% success rate in placing 2–3 fiducials per patient was reported. One case of mild pancreatitis and one fiducial migration were observed [377]. High success rates were also reported for EUS-guided placement of gold fiducials in malignant gastrointestinal lesions [372, 373] and for primary and recurrent prostate cancer [374, 375]. Similar results from experienced centers were reported [378, 379], with adverse event rates at 2% and migration rates 7% and with 91% of the patients able to undergo stereotactic radiation therapy guided by the EUS-placed fiducials [379]. EUS-guided placement of fiducials has also been described to guide parenchymal-sparing pancreatic surgery of small pancreatic neuroendocrine tumors [380].

Two major problems of the EUS-guided placement of fiducials are migration before beginning the targeted image-guided radiation treatment and deviation from ideal fiducial geometry. Comparison of surgical and EUS-guided fiducial implantation in locally advanced pancreatic cancer was performed. The ideal fiducial geometry was more often achieved with surgical placement compared with the EUS-guided approach (47% vs. 18%). Nevertheless, the success rate of fiducial tracking for Cyberknife therapy was equally high in both groups (82% vs. 90%) [381]. A comparative analysis of traditional fiducials (5 mm length and 0.8 mm diameter) and Visicoil fiducials (Core oncology, Santa Barbara, CA; 10 mm length and 0.35 mm diameter) implanted under EUS guidance demonstrated that the mean migration was not significantly different [382]. A report of the insertion of two different designs of fiducials, the Visicoil and the Gold Anchor fiducial (Naslund Medical AB, Huddinge, Sweden), using a 22G needle and the transduodenal route (n = 23) encountered technical difficulties in 11.3% of cases typically in the unloading of the Gold Anchor fiducials. A total migration rate of 9.5% was observed, predominantly of Visicoil fiducials. 95% of patients were able to undergo image-guided radiation therapy, and the infection rate was negligible even without prophylactic antibiotics [383].

Depending on the type of fiducial, 22G and 19G needles can be used for application. Currently fiducials have been front-loaded into EUS needles and injected using the stylet or a water jet. However, a new 22G needle prototype preloaded with four gold fiducials was shown to provide quick, easy and safe fiducial deployment in an animal study [384]. The development of dedicated fiducial needles may help integrate fiducial placement for image-guided radiation therapy in the clinical workflow and as a routine component of EUS.
Recommendation 35

EUS-guided local ablative procedures for pancreatic cystic neoplasms are not recommended outside experimental protocols (LoE 2b, GoR B). Strong consensus (100%).

Recommendation 36

Ablation of symptomatic insulinoma by EUS-guided ethanol injection should be considered in patients not suitable for surgery in whom medical treatment is insufficient to control symptoms (LoE 4, GoR C). Strong consensus (100%).

Recommendation 37

EUS-guided placement of fiducials for image-guided radiation therapy is safe and technically feasible in locally advanced cancer, as an alternative to surgical or image-guided percutaneous placement (LoE 2b, GoR B). Strong consensus (100%).

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Guidelines
