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 diagnostic and 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]. In 1996, the first case series of endoscopic ultrasound (EUS)-guided CPN was reported [8]. The anatomical location of the celiacplexus around the origin of the celiac trunk and the superior mesenteric 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 vi-
sualization by EUS allows direct injection [13] in approximately 80% of cases [9–12].

**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). 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 [4, 15–20].

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

**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 that 80% of patients experienced pain relief [21]. A 5-study meta-analysis (119 patients) demonstrated efficacy of EUS-guided CPN in 72.5% [22]. 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 compared to the conventional management group [23].

**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 [24]. A study of 50 patients with pancreatic cancer randomized to receive single or bilateral injections of alcohol did not observe any difference in onset or duration of pain relief [25].

**Direct celiac ganglia neurolysis**

Visualization of the ganglia is possible in approximately 80% of patients [9–12]. 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%) [26].

**Other technical aspects**

The injected volume of alcohol does not have a significant influence. In patients with pancreatic cancer, EUS-guided CPN using either 10 ml or 20 ml of absolute alcohol had similar efficacy and safety [27]. Performing EUS-guided CPN in patients with non-resectable pancreatic cancer early after diagnosis may provide better pain relief than late salvage therapy [23, 28].

**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%)

**EUS-guided celiac plexus block in patients with chronic pancreatitis**

Two systematic reviews reported on the efficacy of steroid-based EUS-guided CPN 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% [22] and 60% of the patients, respectively [21]. 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 [29].

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 [30]. 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 [31].

**Recommendation 5**

EUS-guided CPB induces moderate pain improvement compared to analgesic drugs only (LoE 2a, 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) [32]. 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 [33].

Recommendation 6
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 [6, 34, 35]. 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) [35].

Recommendation 7:
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%)

Recommendation 8:
Antibiotic prophylaxis should be considered before EUS-guided CPB when steroids are used (LoE 5, GoR C). Strong consensus (100%)

EUS-guided vascular interventions
Background
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 [36–39]. EUS can identify rare causes of gastrointestinal bleeding, e.g. arterial pseudoaneurysm [40–44] and Dieulafoy lesions [45].

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 [46]. 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 [47]. Comparable results have been reported in a case series [48]. Efficacy of EUS-guided coil vs. cyanoacrylate therapy has been compared in consecutive patients with gastric varices. EUS-guided coil application required fewer endoscopies and reported fewer adverse events compared with EUS-guided cyanoacrylate injection [49].

Treatment of non-variceal bleeding
Case series and single cases report successful EUS-guided treatment of non-variceal bleeding from peptic ulcer disease, Dieula-

Pseudoaneurysm therapy and other vascular procedures
Single reports demonstrate successful EUS-guided injection treatment, with cyanoacrylate, vascular coils, absolute alcohol, or 500 IU thrombin directly into pseudoaneurysms of the splenic and superior mesenteric artery where conventional therapy has failed [46, 51–58].

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. The revised Atlanta classification categorizes PFC as acute peri-pancreatic fluid collection (APFC), pancreatic pseudocyst (PPC), acute necrotic collection (ANC) and walled-off pancreatic necrosis (WOPN) [59].

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 [60, 61]. 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 [62–66].

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 [67]. The rate of spontaneous regression is lower in chronic PPC, reported at ≤10% [68]. Drainage is considered if collections become symptomatic or infected [69–73]. Infected collections may be sampled by EUS-guided fine needle aspiration (EUS-FNA) to obtain microbial analysis, which guides antibiotic treatment [74, 75]. With a sterile collection, luminal or biliary extrinsic compression and persistent severe abdominal pain are indications for drainage [61, 76, 77].
stents have been developed that can be deployed in a single step 
following successful endoscopic drainage or those not meeting 
the criteria for endoscopic or percutaneous drainage. The clinical 
outcomes in the case of EUS-guided drainage of WOPN are gener-
ally inferior to PPC. A retrospective study reported a treatment 
success rate of 94 % for sterile and infected PPC versus 63 % for 
WOPN [134, 135]. Mean clinical success rates of 81 % to 88 % and 
EUS-guided drainage is the 
preferred modality when there is no visible luminal bulge or 
when there is a clinical suspicion of portal hypertension and col-
laterals or in coagulopathy [128 – 132].

Recommendation 17

The particular drainage technique for PPC should be chosen in 
consideration of location, infection and/or portal hyperten-
sion (LoE 5, GoR D). Strong consensus (100%)

Recommendation 18

EUS guidance should be preferred for the transmural drainage 
of PPC and other PFC (e.g. WOPN), in particular in the absence 
of luminal bulging and in the case of portal hypertension (LoE 1b, GoR B). Strong consensus (100%)

Walled-off pancreatic necrosis

Over the last 10 years endoscopic drainage has become impor-
tant in the treatment of WOPN with a comparable efficacy to sur-
gical drainage with lower costs and a shorter hospital stay [133]. 
Surgical drainage is reserved for endoscopic failures, recurrence 
following successful endoscopic drainage or those not meeting 
the criteria for endoscopic or percutaneous drainage. The clinical 
outcomes in the case of EUS-guided drainage of WOPN are gener-
ally inferior to PPC. A retrospective study reported a treatment 
success rate of 94 % for sterile and infected PPC versus 63 % for 
WOPN [134, 135]. Mean clinical success rates of 81 % to 88 % and 

EUS-guided drainage technique

EUS-guided drainage is suitable for pancreatic collections abut-
ting the gastric or duodenal wall where a transgastric or trans-
duodenal approach is feasible. Two types of linear echoen-
doscopes are available for EUS-guided PFC drainage: i) a traditional 
side-viewing longitudinal echoendoscope and ii) a forward-
viewing echoendoscope specifically made for interventional pro-
cedures. No difference in outcome between the echoendoscopes 
has been documented [78]. EUS-guided drainage is performed ei-
ther by a multistep or by a one-step procedure, usually guided by 
fluoroscopy [18, 79 – 85]. EUS-guided PFC drainage is also feasi-
ble without fluoroscopic guidance [86 – 88].
A variety of stents have been used to maintain patency of the fisi-
tulous tract between the gut lumen and the PFC: single plastic 
stents (straight or double pigtail), multiple plastic stents, naso-
cystic drainage catheters, enteral metal stents and biliary metal 
stents [18, 81, 82, 85, 89 – 100]. Expandable metal stents have a 
shorter procedure time, documented in an RCT [101] and a 
meta-analysis [102]. PFC drainage by self-expandable metal stents improved clinical success and decreased the adverse event 
rate compared with PFC drainage by plastic stents [99]. Novel lu-
men-apposing self-expandable metal stents and other dedicated 
stents have been developed that can be deployed in a single step 
for PFC drainage [98, 101, 103 – 119].
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 [124, 136, 137]. Combining all available non-surgical drainage techniques (trans-papillary, transmural, percutaneous) gives an overall success rate of up to 94% [126]. A meta-analysis documented a median of 4.09 drainage procedures to be necessary for effective transmural necrosectomy of WOPN [136]. The number of endoscopic sessions is dependent on the size of the collection and the amount of solid debris [65]. 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 [126, 137–148], EUS-guided creation of multiple transluminal gateways for WOPN achieves successful response in 92% [91]. Analysis of the factors impacting the results of the endoscopic treatment of WOPN found multiple transluminal gateway treatment was more successful than conventional single gateway access (94% vs. 62%) [149]. The optimal strategy in WOPN is a “tailored” minimally invasive approach, based on the collection size, location and stepwise response to intervention [147, 150, 151].

**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 [125, 149, 152–154]. Pancreatic ductal leak or disconnection was shown to be significantly associated with PPC resolution failure at 3 weeks [155]. Results of several prospective and retrospective studies suggest long-term transmural stenting in WOPN, in particular in patients with pancreatic ductal leaks or disruption [149, 153, 154].

**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 range from 0–26% [102, 135, 156, 157], most frequently bleeding (2%), perforation (1.6%), secondary infection (4%) and stent migration. Few procedure-related mortality cases have been reported mainly due to bleeding [1, 8, 9]. Severe bleeding events occurred following erosion of the splenic and gastroduodenal artery [134] or following rupture of a visceral pseudoaneurysm [126, 158, 159]. Vascular derangements subsequent to acute pancreatitis must be excluded before performing transmural drainage [160]. Secondary infection arises from contamination of an incompletely drained PFC, from premature stent occlusion, stent dislocation, or uneven collapse [152, 161–164]. In WOPN compared to PPC, procedure complexity and a serious underlying clinical condition increase the morbidity and mortality [35, 135, 136, 165]. 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% of cases [136]. 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% [137]. A consensus report from the USA suggests that management of patients with WOPN should only be performed in high-volume centers with specialized experience in interventional endoscopy and radiology, intensive care, and surgery [143].

**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**

EUS-guided drainage of non-pancreatic fluid collections may be as safe and effective as percutaneous or operative drainage [166]. 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% [124].

**Technique**

The technique does not differ from the EUS-guided PFC drainage. Mediastinal abscesses can be drained by EUS guidance with either plastic or self-expandable metal stents [167–170], along...
with abdominal abscesses (hepatic, perihepatic, subphrenic and splenic) and other fluid collections, e.g. bilomas, hematomas or inflammatory collections [168, 171 – 182]. The technique is particularly valuable for the management of postoperative intra-abdominal fluid collections after intended curative surgery or liver transplantation [168, 174, 175, 178, 180]. 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 [180, 183 – 192]. Drainage routes can be transesophageal, transgastric or transcolonic (transrectal), depending on the relationship between the collection and the gastrointestinal tract [175]. Metallic stents may be preferred due to the decreased risk of leakage or occlusion [182].

**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

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**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 cholangiodrainage and/or surgical intervention (LoE 2b, GoR B). Strong consensus (100 %)
for both methods [220]. 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 rates 94.9% vs. 83.8%) [221]. A rarely used approach, with pooled 77% success (30/39 cases) is the transhepatic access followed by an intraductal anterograde drainage or dilatation of strictures of the bile duct, papilla, or biliointestinal anastomoses [214, 222 – 224], which may then be combined with transluminal intrahepatic drainage procedures [225].

**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%)

**Recommendation 28**

For ESC-D, guidance and documentation by EUS and fluoroscopy should be available (LoE 5, GoR D). Strong consensus (100%)

**Recommendation 29**

The choice of stent (plastic vs. metal) is dependent on the experience of the operator and the access route. If metal stents are used, only partially covered stents are recommended to prevent biliary leakage (LOE 3b, GoR B). Strong consensus (100%)

**Adverse events**

An adverse event rate of 29% (range 3 – 77%) and a mortality rate of 3% are reported for ESC-D [124]. A systematic review of 20 papers [35] reported higher adverse event rates for the intrahepatic access route (18%), compared to the extrahepatic access route (14%). With the drainage technique, the rendezvous technique resulted in an adverse event rate of 11%, while the transluminal drainage adverse event rate was 21% [35]. Comparable results were obtained in a separate review [207]. Lower adverse events are reported by experienced centers [223, 224, 226, 227]. Comparative analysis of two prospective studies suggests that the rate of adverse events may be reduced by a defined algorithm of guidewire manipulation, aiming at replacing EUS-guided retrograde transluminal drainage by rendezvous techniques or anterograde internal approach [224, 228].

A multicenter trial showed a significant advantage of covered metal stents over plastic stents in terms of reduced frequency of biliary leakage (4% vs. 11%) [229].

**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%)

**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 [230 – 232]. EUS-guided gallbladder drainage is a valuable alternative to non-surgical percutaneous or trans-papillary access techniques in patients with acute cholecystitis, who are poor candidates for surgery [233 – 239]. Pooled data reported 98% technical and 99% clinical success rates, with adverse events occurring in < 8% [232]. Similar technical and clinical success rates, but lower pain scores, were reported for EUS-guided gallbladder drainage in prospective comparison to percutaneous gallbladder drainage [240].

**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 pancreatography/drainage**

**Background**

EUS-guided pancreatography was first described in a patient with a symptomatic pancreatic duct stone after pancreaticoduodenectomy [241], followed by a few further reports describing EUS-guided access and interventions of the main pancreatic duct [124, 242].

**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 is performed using needles and guidewires through the echoendoscope. The reported clinical success rate is approximately 75% (range 53 – 100%) [124], with the adverse event rate reported at 19% [242], reflecting the technical challenges of this technique where re-interventions are often necessary [243].

**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%)
EUS-guided tumor ablation therapy

Recommendation 34
EUS-guided pancreatography/drainage should be performed only in referral centers by experienced interventional endoscopists, after multidisciplinary evaluation of alternative therapeutic strategies (LoE 5, GoR C). Strong consensus (100%).

EUS-guided ethanol ablation

Cystic pancreatic lesions
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 [244]. 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 [244–249]. Other studies have combined ethanol lavage with injection of Paclitaxel, a viscous, hydrophobic chemotherapeutic agent believed to have a prolonged effect [250–253]. 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 ethanol ablation [254]. Abdominal pain (mean, 6.5%) and pancreatitis (mean, 3.9%) were the most frequent complications [254].

Pancreatic neuroendocrine tumors
EUS-guided ethanol ablation of symptomatic sporadic insulinoma (size range 5–21 mm) using 95–98% ethanol was reported in 13 patients not fit for surgery. 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 [255–260]. Successful EUS-guided ethanol injection treatment has been described also in pancreatic neuroendocrine tumors in a patient with MEN 1 [261], solitary metastatic lymph nodes [262, 263], gastrointestinal stromal tumor [264], solitary hepatic metastases [265, 266] and left adrenal metastasis [267].

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 [268], dendritic cells [269–271], TNFerade, a replication deficient adenovirus that expresses the tumor necrosis factor alpha [272–274], and Onyx-015, a selective adenovirus that preferentially replicates inside malignant cells [275]. Due to a substantial lack of efficacy despite the minimal number of adverse events encountered, these techniques have not become established in clinical practice.

EUS-guided radiofrequency ablation
RFA is used to ablate neoplastic tissue by local thermal-induced coagulative necrosis of the tumor [276]. Results and safety of EUS-guided RFA (liver, pancreas, lymph nodes) have been evaluated only in animal experiments with encouraging results [277–281], and only in a few human patients with pancreatic tumors [282, 283].

EUS-guided interstitial brachytherapy
EUS guidance can also be used to implant intra-tumoral radioactive seeds [284, 285]. The clinical efficacy and safety of EUS-guided implantation of radioactive I125 seeds in advanced pancreatic cancer was evaluated with routine gemcitabine-based 5-FU chemotherapy 1 week after brachytherapy [286]. Compared with brachytherapy alone [287], the combination of chemotherapy and radioactive I125 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 [287].

EUS-guided intratumoral placement of fiducial markers
Fiducial markers include radioopaque spheres, coils, or seeds that are implanted in or near the tumor to guide stereotactic body radiation therapy. EUS-guided fiducial placement has been reported to be feasible and safe in several studies of inoperable pancreatic [288–293], adrenal [293–296] or mediastinal malignancy [284, 294] and for primary and recurrent prostate cancer [297, 298]. The reported success rate is between 84.6% to 100%, and adverse events are few (7/278, 2.5%) and limited to mild pancreatitis, abdominal pain and infection [124]. Problems of EUS-guided placement of fiducials are migration before beginning targeted image-guided radiation treatment (in approximately 7%) and deviation from ideal fiducial geometry [289–292, 299]. Depending on the type of fiducial, 22G and 19G needles can be used for application.

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 which 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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