EUS-Guided Interventions: Indications, Contraindications, and Risks

Stefan Hollerbach and Christian Jürgensen

G. Kähler et al. (eds.), *Therapeutic Endoscopy in the Gastrointestinal Tract*,
https://doi.org/10.1007/978-3-319-55468-6_5

5.1 Endosonography-Guided Fine-Needle Puncture (EUS-FNP): Indications, Value, and Evidence of Endosonography-Guided Fine–Needle Interventions

General Considerations and Description of the Method

The term endoscopic ultrasound-guided fine-needle puncture (EUS-FNP) includes all endosonographic methods to gain material by the use of biopsy needles such as fine-needle aspiration (needle diameter 19–25G) and Trucut biopsy (=EUS-TCB, diameter 19G). EUS-FNP enables us to gain material out of structures which are otherwise not or only at high risk accessible. The cytohistologic results are of relevance for many patients in terms of diagnosis, prognosis, and further therapeutic treatment. EUS-FNP is the method of choice for the initial tissue-based diagnostic workup of lesions of or around the gastrointestinal tract, for staging of malignant tumors, and for the differential diagnosis of numerous benign diseases.

Despite being judged as minimally invasive, EUS-FNP should be used only if an obvious indication and clinical consequences from the results are given (Dumonceau et al. 2011; Jenssen et al. 2011a; Jenssen and Hollerbach 2013; Hollerbach et al. 2003, 2010). The results should influence the further clinical course of the individual patient, such as neoadjuvant chemotherapy vs initial surgery or directing tumor therapy of malignancies such as lymphoma, GIST, or other diseases.

Personnel, Instrumentation, and Organizational Requirements

A detailed written informed consent obtained by a physician is a legal prerequisite for EUS-FNP (as it is for other endoscopic interventions). Before beginning the procedure, all clinical and anamnestic data of the patient should be present, such as images and reports of previous radiologic and endoscopic examinations or histology reports. Additionally, the examiner should be aware of patient-specific risk factors. This approach enables him to take the whole clinical situation into account.

Personnel Requirements

Interventional endosonography should be performed only by physicians who are experienced with the method. Additionally, it is expensive. Therefore, it is only cost-effective for specialized centers performing more than 100 EUS-FNP interventions per year. The performing physician should be familiar with the use of side-viewing endoscopy and with clinical ultrasound diagnosis. Additionally, he should be able to handle complications such as bleeding or defects of the gastrointestinal wall. Sedation should be performed according to the local national guidelines. According to the German S3 guideline for sedation, one trained nurse cares for the surveillance of the patient (NAPS), while the second assists the physician performing the EUS procedure. In specific situations such as an ASA-III-patient, difficult EUS procedure, a second physician may be needed. These requirements should be taken into consideration when planning the interventions. If the obtained material is processed adequately, there is no need for an onsite pathologist.

Instrumental Requirements

For EUS-guided interventions, linear scanner side-viewing instruments are a prerequisite. They offer the option to perform interventions under ultrasound guidance. Three companies offer suitable instruments (Hitachi–Pentax, Fujinon, Olympus). Digital video endoscopes, when connected with light source and processor, produce endoscopic and ultrasound images, which are transmitted to monitors. The Albarran elevator of interventional instruments offers the option to angulate instruments introduced into the working channel. Most digital echoendoscopes have an oblique side-viewing optic and an ultrasound unit at the tip of the instrument. They differ in size and position of the ultrasound unit, size of the working channel (2–3.8 mm), size and type of adapted ultrasound unit, and electronic image resolution.

The curved-array transducer produces a 120°- or 170°-sector ultrasound image oriented in the longitudinal axis. As a result, every step of the procedure performed via the working channel can be observed under direct endosonographic surveillance. The ultrasound frequency, usually in the range of 5–12 MHz, can be adapted. The coupling of the ultrasound is optimized by a water-filled balloon at the tip with minimization of interfering air bubbles.

All instruments are equipped with a color Doppler and a continuous wave (CW) Doppler to offer the option of differentiated analysis of vessels.

Further detailed descriptions of instruments would lead too far. They are provided by manufacturers of echoendoscopes.

For EUS-FNP, the following instruments are needed:

- Balloons for the ultrasound unit (water coupling, protection)
- Standard EUS-needles for fine-needle puncture (19–25 gauge in diameter with stylet)
- Suction syringe for aspiration (e.g., Hepafix)
- 10–20 ml of sterile saline 0.9% solution (to flush the needle after use)
- Formalin container (for fixation of tissue)
- Microscope slides ± fixation spray for cytology

Organizational Requirements

The technical and personnel needs of interventional endosonography are high. Every intervention should be planned in advance involving the patient and the team. Needs in terms of room, time, and additional instruments should be part of the daily team session. Especially in advance of therapeutic maneuvers such as drainage procedures, interfering influences such as ringing cell phones or uninvolved people passing the room should be eliminated.

The Procedure of EUS-FNP

The EUS-FNP is performed in left lateral position (as in gastroscopy), while the patient is sedated, i.e., by a combination of propofol and midazolam. An analgosedation may be needed for therapeutic procedures. If the procedure takes longer, special attention should be focused on the avoidance of positional damage. Topical pharyngeal anesthetics such as lidocaine spray and sedating drugs (i.e., propofol, pethidine, midazolam) are used as known from standard endoscopic procedures. Oxygen saturation and blood pressure are part of the patient's supervision. Electrocardiogram surveillance is part of the surveillance in risk patients. Additional oxygen via nasal tube should be available. Optimal oxygen supply and minimal resistance of the patient is the goal to allow a safe passage of the endoscope into the stomach. Antibiotic prophylaxis in advance is indicated for patients with personal high risks (such as artificial heart valves) or if extraluminal fluid collections are addressed. Suitable antibiotics are, for instance, amoxicillin, ampicillin, ceftriaxone, ciprofloxacin, or cefuroxime. Special extraction methods such as needle-based brush cytology, special transport media for microbiology, or molecular biology should be prepared in advance.

Indications, Value, and Evidence of EUS- FNP

EUS-FNP has a big impact on visceral medicine in terms of tissue-based diagnostic and tumor staging. By fine-needle puncture, you can achieve more than 1,000 cells for further histologic and cytological examination (for example, paraffin hybrid techniques). EUS-FNP has a high, but examiner-dependent diagnostic accuracy for lesions of the mediastinum, perigastric area, retroperitoneum, and the perirectal space. After initial difficulties, a medium sensitivity of 85–95% can be achieved for suspected lesions of the mediastinum, around the esophagus, stomach, and rectum, as well as for the liver hilum, parts of the liver, the distal bile duct, and the pancreas (Dumonceau et al. 2011; Jenssen et al. 2011a; Jenssen and Hollerbach 2013; Hollerbach et al. 2003, 2010). The reported specificity of 95–100% is high, especially if all additional histopathological methods such as immunohistochemistry, FACS, phenotyping, tumor marker, and surface antigens are part of the spectrum. Details should be discussed with the corresponding local pathologist. Capabilities of fine-needle puncture reach their limit if the method is overextended. This could be the case when puncturing a fibrotic or calcified lymph node or pancreatic tissue. The aspiration of little tissue particles is determined by physical limits. Improvement of cut needles to gain bigger tissue particles for histology is needed.

It is feasible to obtain tissue by EUS-FNP even for lesions smaller than 5 mm. Therefore, the method is particularly suitable for the N-staging of tumors such as lung cancer. Even the diagnostic of malignant lymphomas (HL, NHL) by EUS-FNP is possible, if clinicians and pathologist keep in close contact. EUS-FNP is essential for modern stage-adapted tumor therapy (lung, gastric, and pancreatic cancer, pancreatic NET, and lymphomas). It has impact on the therapeutic approach such as stage-adapted neoadjuvant tumor therapy of stomach and rectum. EUS diagnostic is based on morphology (tumor extent, depth of infiltration, involvement of adjacent structures) and, if clinically indicated, on tissue by cytohistologic biopsy.

Benign and malign mediastinal, retroperitoneal, and perirectal lesions (such as lymphomas, tuberculosis, sarcoidosis, subepithelial lesions) are another indication for rapid histologic diagnosis.

These lesions of the gastrointestinal wall or its surroundings were previously detected by endoscopy (gastroscopy, colonoscopy), by radiology (MRI, CT, X-ray) or by percutaneous ultrasound.

The main indications for EUS-FNP are provided in Table 5.1. The range of indication is mainly dependent on the depth of introduction of the echoendoscope, which usually ends at the

Table 5.1 Indications for EUS-FNA in the posterior mediastinum and/or in the upper and lower GI tract

Mediastinum
Primary diagnosis lung cancer: Cytohistological diagnosis of lung cancer, lymph node metastasis, distant mets
Mediastinal lymph node staging: histologic proof of N2 or N3 situation (NSCLC); proof of any nodal cancer involvement independent of localization (SCLC)
Infradiaphragmatic metastasis in lung cancer: proof of M- situation (i.e., left or right liver lobe, adrenal glands, infradiaphragmatic lymph nodes)
Restaging after neoadjuvant therapy: selected patients with curative therapeutic intention, for instance, patients with NSCLC stage SIII (N2 + /N3 +) following neoadjuvant therapy that may undergo subsequent surgery
Primary diagnosis of other pathologic mediastinal /pulmonary lesions such as tumors, metastasis of unknown origin, indistinct lymphadenopathy, fluid collections/abscesses in the posterior mediastinum (including Hodgkin´s disease, non-Hodgkin's lymphoma, thymoma, germ cell malignancies, esophageal cancer, sarcoidosis, tuberculosis, actinomycosis and others)
Esophagus/cardia/stomach/duodenum
Local *T-, N-, and M- staging* of esophageal, cardiac, gastric, biliary, and pancreatic cancer including their specific surrounding lymph node regions
Primary diagnosis: if failure of simple biopsy methods, in case of contraindications for other diagnostic methods, for instance, in cases with linitis plastica, cancer of bile ducts, or gall bladder cancer
Primary diagnosis and *staging* of subepithelial tumors (SET), i.e., esophageal, gastric, and duodenal tumors including GIST, leiomyoma, leurinoma, lipoma, Abrikosoff tumors, cystic tumors, and others
Primary diagnosis and local *staging*: indistinct abdominal or retroperitoneal lymph node disease/adenopathy
Primary diagnosis and local *staging* of peritoneal tumors, metastasis, lymph nodes, abscess formations and fluid collections including lymphomas, Ormond´s disease, metastasis, inflammatory masses, abscesses, walled-off necrosis, and others
Primary diagnosis and local *staging* of adrenal gland including oncologic and/or endocrinologic cases
Primary diagnosis and local *staging* of lesions at level of Vater´s papilla and/or the extrahepatic portion of the biliary tree including papillary adenomas, adenomyomatosis/«papillitis stenosans,» carcinoma of Vater´s papilla, biliary stones, locoregional, lymph node staging, ductal abnormalities (such as pancreas divisum)
Primary diagnosis and local *staging* of malignancies located in the biliary system and other digestive organs including liver metastasis, malignant ascites, pleural effusions, adrenal gland metastasis, mediastinal lymph node metastasis, indifferent pathologic lesions in accessible parts of the liver and central hilar structures (i.e., metastasis, HCC, CCC)
Primary diagnosis and local *staging* of lesions located in or around the spleen such as abscesses, NHL, Hodgkin´s disease, metastasis, and lesions located in accessible parts of both kidneys
EUS Indication: Lower GI Tract
Staging: locoregional N-staging of lymph nodes of rectal carcinoma
Primary diagnosis: submucosal tumors in/around the rectosigmoid colon
Follow-up: histologic proof of extraluminal recurrences /relapse in CRC and in other GI-malignancies
Primary diagnosis: abscesses and unclear processes located in the lower pelvis
Miscellaneous: prostatic or uterus lesions and/or ovarian/vesicular lesions (selected cases)

Table 5.2 Indications for EUS-FNA in pancreatic malignancies

Non-resectable tumors
Cytologic/histologic diagnosis prior to chemotherapy
Proof of non-resectability (liver metastasis, mediastinal lymph node metastasis, pleura- and peritoneal carcinosis)
Resectable tumors
Suspected solid neoplasia other than ductal adenocarcinoma, i.e., neuroendocrine tumors, malignant lymphoma, pancreatic metastasis
Differentiation and risk assessment of cystic pancreatic lesions
Suspected ductal adenocarcinoma, if patient´s decision for subsequent surgical therapy depends on cytopathologic proof of malignant disease or if neoadjuvant treatment studies are on their way
Unspecific findings
Cytologic/histologic diagnosis proof and differentiation of malignancy in case of low pretest probability for a malignant tumor, for instance, in focal pancreatitis, autoimmune pancreatitis, and others

descending duodenum (upper GIT) or distal sigmoid (lower GIT).

EUS-FNP for Initial Diagnosis

The differential diagnosis of mediastinal or retroperitoneal lymphadenopathy in patients with or without an underlying malignancy could be a challenge. The differential diagnosis can be insufficient or even impossible based on morphologic criteria. It includes unspecific reactive and inflammatory lymph node enlargements, pneumoconiosis, granulomatous diseases (sarcoidosis, tuberculosis, other mycobacterial diseases, mycosis), as well as malignant lymphomas and metastasis of a known or unknown other malignancy (Jenssen and Hollerbach 2013; Hollerbach et al. 2003, 2010).

Having less invasiveness compared to mediastinoscopy and VATS, EUS-FNP has a high power to clarify the nature of unspecified mediastinal lymphadenopathy or other lesions. To tap the full potential, it should include all histologic, immunochemical, molecular-biological, and bacteriological methods (Table 5.1). A close collaboration with the corresponding laboratory and pathology physician and the use of appropriate transport media for specialized examination is crucial.

Likewise, EUS-FNP can be used for difficult accessible lesions of the retroperitoneum (including adrenal gland, kidney, pancreas), of the spleen, and of the left liver lobe including the liver hilum (Table 5.2, Fig. 5.1). Additionally, para-aortic lymph nodes and lesions such as morbus Ormond are accessible up to the level of the aortic bifurcation using a transduodenal approach. EUS-FNP should be taken into account if liver lesions are not clarified by contrast imaging and are not accessible transcutaneously (Dumonceau et al. 2011; Adler et al. 2007).

Solid masses of the adrenal glands most often consist of nonfunctional, benign adenomas or hyperplastic nodules that do not require any histologic assessment (so-called incidentalomas). There are, however, some adrenal masses ranging from 3 to 6 cm in size that may require further workup (according to certain diagnostic algorithms) upon exclusion of hormonal activity from these tumors. EUS-guided fine-needle aspiration (or core-needle) biopsy (EUS-FNA) should only be performed after pheochromocytoma has been ruled out, for instance, by 24-h-sampling of urine to measure catecholamine and metanephrine levels. Most EUS-FNA biopsies with cytohistologic analysis are being carried out to search for metastasis into the adrenal glands in lung cancer, colonic cancer, and others. The left adrenal gland is readily accessible for EUS-FNA in virtually all cases (Fig. 5.2), while the right adrenal gland shows variable accessibility and cannot be seen by EUS in approximately 30–40% of cases.

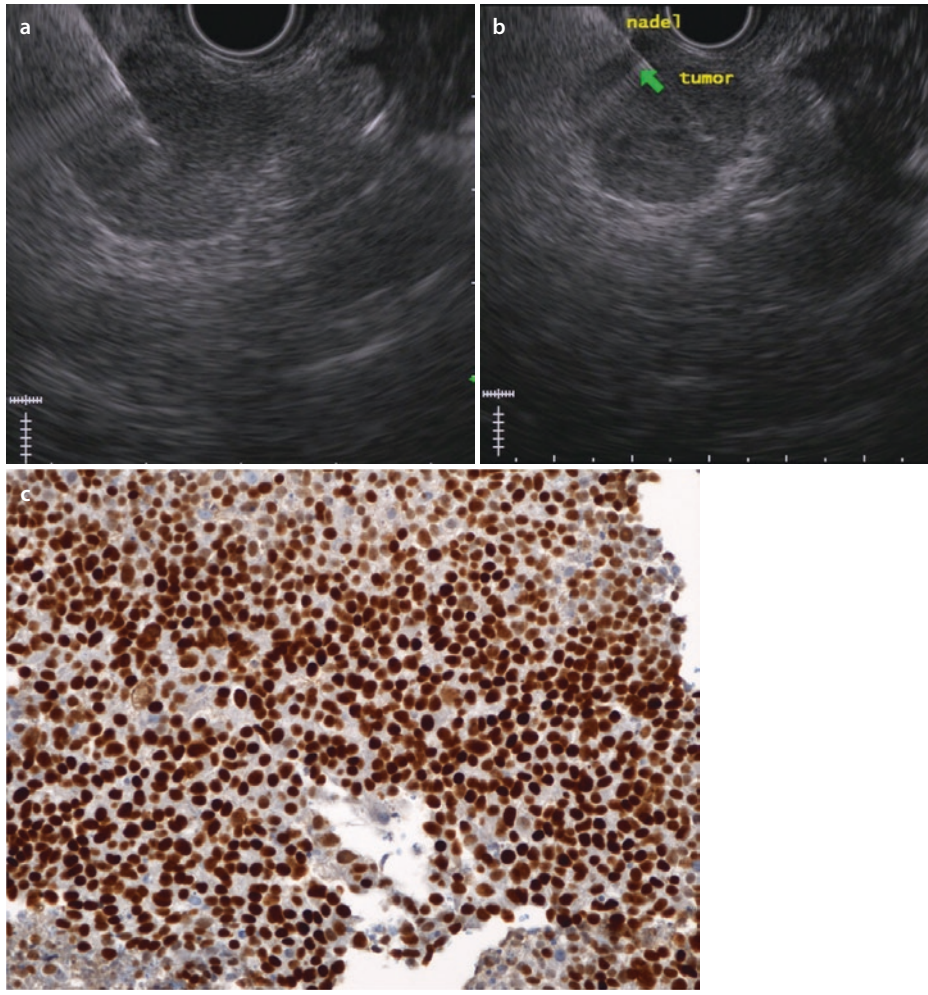

Fig. 5.1 **a** EUS-FNP of a small tumor of the pancreatic head. **b** Additionally, the position of the needle and the ultrasound tip in the duodenum can be seen. **c** The cytohistology confirms the diagnosis of a benign insulinoma

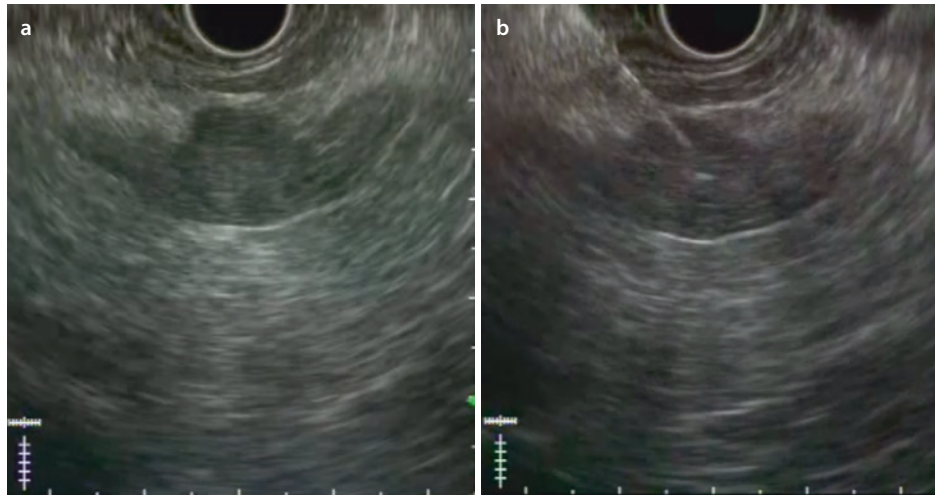

Fig. 5.2 EUS and EUS-FNP of a small metastasis of a colorectal cancer within the left adrenal gland, left adrenal gland with a small protrusion **a**, a metastasis of a colorectal cancer is confirmed by FNP **b**

EUS-FNA for Primary Diagnosis and Assessment of Malignancies

According to evidence-based standards, EUS-FNA is very helpful and indispensable for the primary diagnosis and staging of malignancies such as lung cancer, pancreatic cancer, and other pancreatic neoplasms such as neuroendocrine tumors, lymphoma, GIST, sarcomas, and others (Figs. 5.3 and 5.4). At present, EUS-FNA has replaced many other alternative procedures such as CT-guided or surgical percutaneous biopsies, or ERCP brush cytology specimens (Dumonceau et al. 2011; Jenssen et al. 2011a; Jenssen and Hollerbach 2013; Hollerbach et al. 2003, 2010; Sharples et al. 2012; Adler et al. 2007; Jenssen and Dietrich 2008).

Locoregional staging by EUS-FNA exerts a significant impact on the further clinical decision-making in cancer patients when cytohistologic proof of malignant disease stages a tumor up (or down, if true negative results are revealed). This is frequently the case in patients with lung cancer (NSCLC) – particularly when EUS-FNA reveals metastasis to the adrenal glands or retroperitoneal

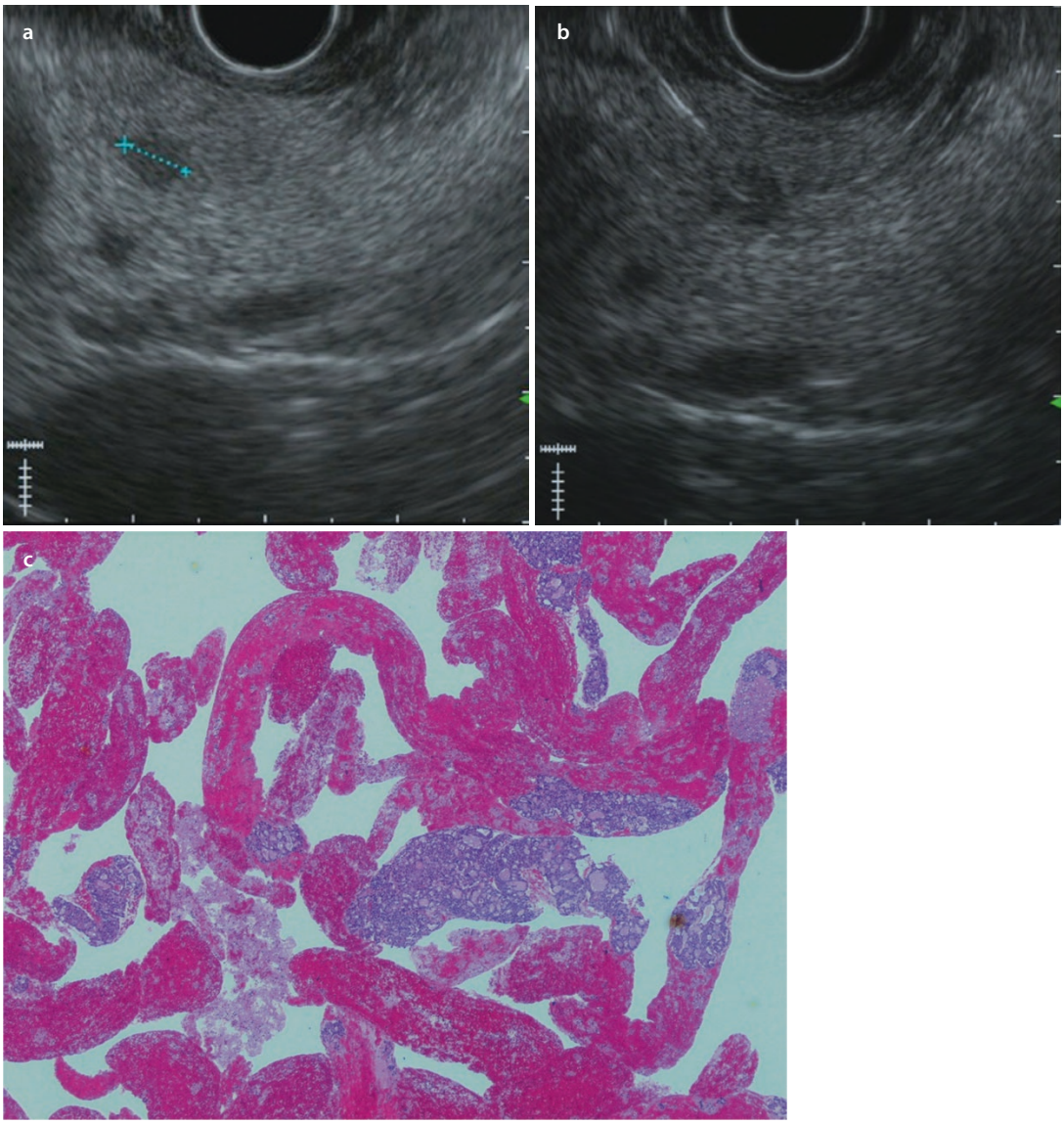

Fig. 5.3 EUS and EUS-FNP of a small pancreatic lesion **a**, which could be diagnosed by EUS-FNP **b** and corresponding cytohistology **c** as a small non-functional neuroendocrine tumor (NET)

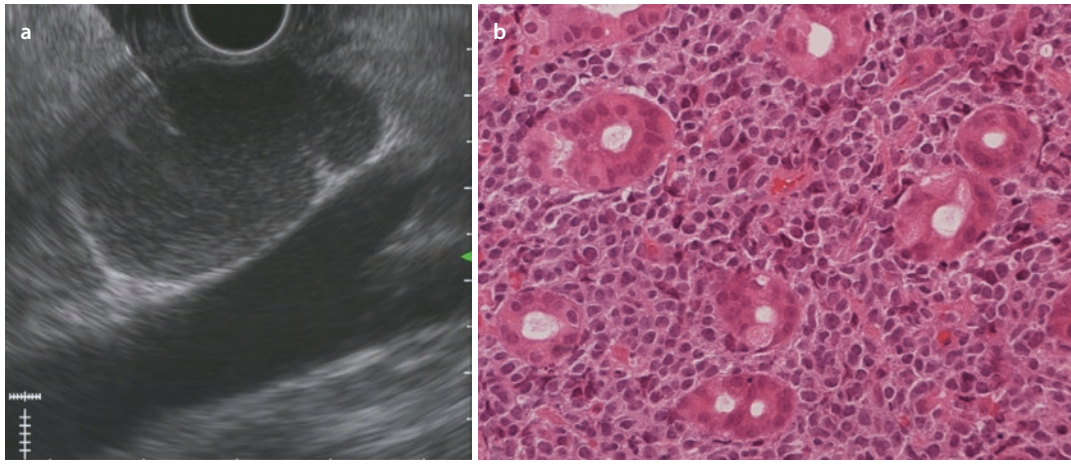

Fig. 5.4 **a** EUS-FNP of a lymphoma of unknown dignity located directly «on» the aorta. **b** The cytohistology confirms the diagnosis of a malign b-cell non-Hodgkin's lymphoma (B-NHL)

lymph nodes or when PET-negative, contralateral lymph nodes have been proved to be infiltrated by cancer (N3 situation). In such circumstances and disease stage, surgical procedures are most often deemed unnecessary and too aggressive since they do not offer any chance of healing to the affected patients but expose the patients to a high risk of postoperative complications (including postoperative mortality ranging from 2% to 4%, pulmonary complications in approximately 15% of cases).

Since both EUS-FNA and EBUS-TBNA exhibit a far superior safety and convenience profile for patients and investigators (when compared with thoracic surgery including mediastinoscopy/thoracotomy), major diagnostic surgery has almost become obsolete. Therefore, most patients do not need any surgical staging procedure. EUS-FNA and EBUS-TBNA are complementary procedures that allow for accurate oncologic tumor staging in almost every patient with lung carcinoma. Up to 25% of patients who are PET-negative do still have carcinomatous infiltrates within their regional lymph node stations, which can be detected by fine-needle biopsy in most instances. Hence, such positive N2- or N3-categories preclude patients from unnecessary operations. EUS-FNA also has the potential to disclose previously undiagnosed distant metastases such as adrenal gland involvement and/or small metastatic nodules in the liver or infradiaphragmatic lymph nodes. In summary, staging of lung carcinoma has been greatly simplified and improved by the use of endoscopic staging procedures including EUS-FNA and EBUS-TBNA (Table 5.2 and Table 5.3) (Jenssen and Hollerbach 2013; Hollerbach et al. 2010; Moehler et al. 2011). Modern contemporary staging concepts reserve surgical mediastinoscopy or VATS for the few remaining clinical cases in which EUS could not be properly performed or which were invariably negative due to technical difficulties or repeated sampling errors (Jenssen and Hollerbach 2013; Sharples et al. 2012). The clinical impact of EUS biopsy results in oncologic treatment algorithms in lung cancer, and other malignancies has been clearly proven by numerous clinical studies and can be considered evidence-based (Sharples et al. 2012).

Table 5.3 Additional clinical indications for EUS-FNA

Masses/suspicious lesions located in the adrenal glands (oncologic and/or endocrinologic queries)
Retroperitoneal masses or lumps (i.e., mesenchymal tumor, paragangliomas, ...)
Liver tumors (particularly HCC) and splenic masses/lesions in patients at increased risk for percutaneous biopsy
Unclear abdominal or retroperitoneal lymph adenopathy
Suspicion of retroperitoneal abscess

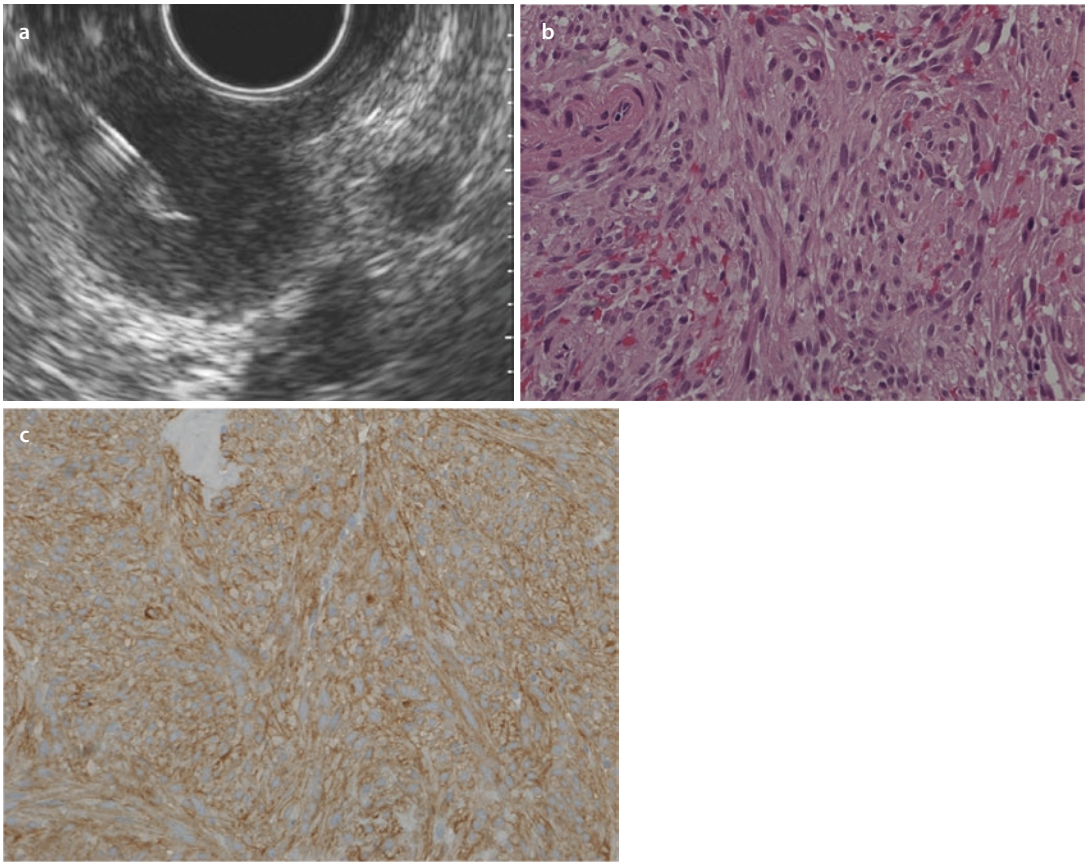

Fig. 5.5 **a** EUS-FNP of a small echoless subepithelial tumor. **b** A benign gastrointestinal stroma tumor (GIST) could be confirmed by cytohistology, as well as being positive for CD 117 **c**

EUS-FNA is also helpful and accurate for cytohistologic assessment of pancreatic tumors that – based on radiologic or endosonographic imaging findings and surgical judgment – appear to be unresectable at time of diagnosis (Dumonceau et al. 2011; Jenssen et al. 2011a; Moehler et al. 2011). Such findings preclude patients from unnecessary surgery and facilitate decision-making for neoadjuvant or palliative treatment decisions.

Approximately 10–15% of pancreatic tumors are not ductal adenocarcinomas but consist of other malignant (or semi-malignant) entities such as neuroendocrine tumors, metastases, lymphomas, or solid-papillary pancreatic tumors (young women). In all cases of doubt, EUS-FNA can be very helpful to establish a definite diagnosis prior to individual therapy, to rule out benign disease such as autoimmune pancreatitis, to assess prognosis of cancer patients, to plan surgical strategy, and – most recently – to allow for novel therapeutic studies that investigate new regimes for neoadjuvant therapy in pancreatic cancer.

EUS-FNA techniques can be helpful for assessment and definite diagnosis of subepithelial tumors (SET) in the upper and lower GI tract (Fig. 5.5). EUS needles, however, have a limited diagnostic accuracy – particularly in small tumors (<1.5 cm) – that is superior to other approaches such as «button-hole» forceps biopsies during EGD (Dumonceau et al. 2011; Jenssen et al. 2011a; Jenssen and Hollerbach 2013; Jenssen and Dietrich 2008) but still doesn't exceed >65–70% in this setting, which is not satisfying as yet. Accuracy can possibly be enhanced by using novel biopsy devices such as the «shark core» needle, but the potential of such techniques remains to be substantiated by ongoing clinical trials.

In patients suffering from ampullary or biliary neoplasias including bile duct and gall bladder carcinomas, EUS-FNA achieves better results than other diagnostic approaches including brush biopsies or

biliary forceps biopsies. Even small neoplasias are clearly visible and detectable by EUS and can be punctured with high diagnostic accuracy.

In some other malignancies including focal liver tumors such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (CCC), or scirrhous gastric cancer, EUS-FNA can be used (with high diagnostic accuracy) as an alternative technique to obtain histologic proof of disease and tissue-based diagnosis for targeted oncologic therapies and treatment planning (Dumonceau et al. 2011; Jenssen et al. 2011a; Jenssen and Hollerbach 2013; Hollerbach et al. 2010).

EUS-FNA for Lymph Node (N-)Staging in GI Malignancies

EUS-FNA has been proven to play an evidence-based role for the clinical staging of GI malignancies including N-categories. However, its accuracy for the detection and biopsy of malignant lymph nodes is limited by anatomical factors as well as problems of accessibility for fine-needle puncture. As pointed out earlier, EUS-FNA and EBUS-FNA both play a major role for lung cancer staging including N-staging and have an important impact on clinical decision-making in affected patients.

Detection and locoregional biopsy of suspicious retroperitoneal lymph nodes are also very important in other cancers such as biliary carcinoma, hepatocellular carcinoma, and neuroendocrine tumors, as shown in several clinical studies.

In contrast, locoregional involvement of peripancreatic lymph nodes does not change current treatment protocols including radical surgery as single most important measure, whereas novel neoadjuvant treatment studies are currently on their way that may possibly change the dismal clinical course and prognosis of affected patients.

In patients with esophageal, gastric, duodenal, and rectal cancer, however, the overall survival and prognosis are highly dependent on lymph node (micro-)metastasis, as shown in numerous clinical studies. The presence of lymph node spread (= N+ situation) in such cancers dramatically reduces the 5-year survival rate of affected patients by more than 50%. If stage N+ and/or advanced T stages are found during EUS staging in such cancer patients, neoadjuvant treatment protocols should be the strategy of choice in most instances. Therefore, German clinical S3 guidelines recommend EUS staging for esophageal, gastric, and rectal cancer in combination with imaging studies (CT, MRT, PET), whereas the exact role of FNA has not yet been fully addressed in these guidelines. Accuracy of N-staging can be substantially improved by EUS-FNA (Moehler et al. 2011). If FNA is performed by passing the needle through the tumor into a regional lymph node, this biopsy is often contaminated by tumor cells arising within the GI wall layers but not from the lymph node itself (Jenssen et al. 2011a; Levy et al. 2010). This problem must be avoided during EUS-FNA by choosing different pathways for the biopsy needle that do not go straight or laterally through tumor-infiltrated GI layers, and by removing the stylet of the needle only after the needle tip is clearly visible within the lymph node.

Lymph nodes should only be biopsied, however, during EUS staging if the results have a high likelihood to change the individual treatment strategy in all patients, for instance, decisions in favor of palliative versus surgical treatment.

Distant metastasis is only rarely detectable by EUS techniques in GI cancers because of the locoregional character of this technique and limited access to distant organs and compartments. However, in up to 12–15% of EUS staging cases with esophageal, gastric, pancreatic, and biliary cancers, EUS may detect previously unknown – or unclear – focal lesions that were not clearly visible, or mistaken, during CT or MRT imaging (= «obscure» metastasis). Examples include distant suspicious lymph nodes in pancreatobiliary cancer such as mediastinal lesions, small liver metastasis <5 mm in patients with esophageal or gastric or colorectal cancer, small adrenal noduli, pancreatic lesions, and peritoneal or pleural masses. In such cases of doubt, needle biopsy should be undertaken or attempted since histologic proof of advanced disease may dramatically change treatment decisions, including surgical interventions that are no longer indicated. Knowledge of TNM staging classification for each subtype of GI cancer is absolutely necessary (Sobin et al. 2009) before oncologic treatment plans can be made with accurate certainty.

For therapeutic interventions, advanced expertise arising from advanced experiences with EUS techniques is the principal requirement prior to introduction of such techniques. Table 5.4 demonstrates the current status of therapeutic EUS techniques in the clinical setting, of which several techniques should still be regarded as strictly experimental.

Table 5.4 Existing array/options of EUS-guided endoscopic therapy

Clinically established therapeutic EUS procedures
EUS-guided drainage therapy of pancreatic pseudocysts (including stent and other drainage catheter implementation)
EUS-guided celiac plexus neurolysis (EUS-CPN) for pain therapy in malignant pancreatobiliary tumors or chronic pancreatitis (clinical effectiveness – according to definition – between 50 and 80%).
EUS-guided cholangiodrainage (EUS-TCD)
EUS-guided pancreatic duct drainage (EUS-TPD)
Experimental therapeutic EUS procedures
EUS-guided intratumoral injection therapy (EUS-FNI) of malignant cysts and tumors with cytotoxic agents (such as paclitaxel), chemotherapeutics, immune-modulators (i.e., mixed allogenic lymphocyte populations, TNFerade), and others
EUS-guided implantation of «seeds» for local brachytherapy radiation (tumors, celiac plexus) or medications (tumor therapy)
EUS-guided radio-frequency ablation (RFA) of tumors (pancreatic carcinoma, liver metastasis, retroperitoneal tumors)
EUS-guided local laser-, therapy- or photodynamic therapy
EUS-guided botulinum-toxin therapy (Achalasia)
EUS-guided trans-endoscopic surgery (NOTES), for instance, transmural lymph node extraction, gastrojejunostomy, bariatric endoscopy, and others
EUS-guided endoscopic mucosal resection (EUS-EMR)
EUS-guided variceal injection therapy
EUS-guided intravascular therapy (for instance, endo-coils for PA-embolization)

Contraindications and Clinical Risk Profile of EUS-FNA

Thanks to the small needle size and flexibility of modern echoendoscopes, the number of contraindications for EUS-FNA is very low. EUS-FNA has been proven to be a safe and accurate diagnostic technique in humans, which greatly facilitated its widespread use in the Western world. Naturally, all general rules and limitations and contraindications of other routine endoscopic procedures apply the same way to EUS-FNA. These include therapeutic anticoagulation, novel oral anticoagulation substances[1] (NOAK), or clopidogrel and other ADP-antagonists.[2]

In addition, patients with severe plasmatic coagulopathies (INR >1.75, significantly prolonged activated prothrombine time PT), or those presenting with severe thombopenias (thrombocyte count <50,000), should not be deliberately subjected to EUS-FNA in terms of a pre-diagnostic risk assessment. In contrast, aspirin (ASS) treatment is no longer considered to be a major obstacle to EUS-FNA.

Other absolute contraindications of EUS-FNA include lack of informed consent by patients or lack of visibility during needle biopsy. To minimize risk of bleeding, interpolated vessels located within the needle tract should always be avoided during EUS-FNA.

The general clinical condition of the individual patient needs always to be considered, while EUS-FNA is planned during clinical risk assessment strategies. If EUS-FNA results do not look likely to impact further clinical decision-making, its indication should always be critically reassessed. Tables 5.5 and 5.6 demonstrate absolute and relative contraindications for EUS-FNA.

The *overall rate of complications* of diagnostic endosonography (without FNA) is reported to lie somewhere in the range between 0.03% (retrospective questionnaires) and 0.22% (prospective studies). Complications of EUS-FNA are somewhat more frequent: one systematic analysis of 51 EUS-FNA studies including 10,941 patients reported a cumulative complication rates of 0.98%. Looking at the 31 existing prospective studies only, however, sheds a – probably more realistic – light on the clinical situation: in this analysis the cumulative rate of complications reached 1.71% of cases (Polkowski et al. 2012; Wang et al. 2011; Gottschalk et al. 2012; Jenssen et al. 2011b). Similar data could be obtained from the prospective German Endosonography Register, which reported overall complication rates around 2.05% of diagnostic cases (▶ www.eus-degum.de) (Gottschalk et al. 2012). Mortality

1 Including novel anticoagulants such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®).
2 Clopidogrel (Plavix ®, Iscover®), prasugrel (Efient ®), ticagrelor (Brilique®).

Table 5.5 Contraindications for EUS-FNA/EUS-FNI

Absolute contraindications
Missing informed consent of patients
Patient uncooperative, lack of sufficient sedation
Severe coagulopathy
Oral anticoagulation, therapeutic heparin treatment or plasmatic clotting disorders (INR > 2; thrombocyte count <50,000)
Thrombocyte-aggregation inhibitors such as clopidogrel and other ADP antagonists (prasugrel, ticagrelor)
Continued intake of novel anticoagulants such as Xa antagonists (e.g., rivaroxaban) or thrombine antagonists (dabigatran)
Combinations of clotting-impairing substances => reduction on ASS only
Cystic mediastinal lesions
Interposition of large blood vessels
Relative contraindications
Patient cases in whom no significant impact of EUS-FNA results can be expected
Limited visibility/control of FNA needle tip at biopsy
EUS-FNA of hepatic lesions in cases of non-sufficient drainage of obstructed bile ducts

Table 5.6 Risk profile and adverse effects of EUS-guided risk profile and adverse neurolysis therapy (EUS-CPN)

Frequent adverse events (in approximately 20–30% of cases)
Post-interventional small–moderate drop of blood pressure RR (hypotonia): usually self-limiting
Transient diarrhea (1–2 days post intervention)
Local hemorrhage (frequently self-limiting, conservative management)
Mild–moderate pyrexia: frequently self-limiting
Local pain syndrome: frequently short-acting, self-limiting
Rare, serious adverse events (in approximately in 1–3% of cases)
Local infections with abscess formation
Sepsis: particularly reported following local corticosteroid injection
Single cases: GI ischemia/infarction including spleen, small bowel, stomach, colon
Single cases: spinal infarct/transient nerve palsy

rates, in contrast, have only been reported in extremely rare circumstances.

The most frequent adverse events (AE) include light (or moderate) pain, transient lipasemia, fever, and light infectious events. Less frequently, intra- and extraluminal bleedings/hemorrhages have been reported that mostly stopped and resolved spontaneously. Severe adverse events (SAE) such as perforation, biliary, and pancreatic leakages, however, have only rarely been reported (Gottschalk et al. 2012; Jenssen et al. 2011b).

The risk of tumor-cell seeding by EUS-FNA may exist in rare cases, but its clinical significance remains obscure despite some reports in the literature. Evidence is poor since only a few case reports exist, and the clinical consequences of such events have not always been reported.

The design and rigidity of some – mostly earlier endoscope series – echoendoscopes exposes the instrument to a somewhat higher risk of perforation, particularly at natural anatomic narrowings such as hypopharynx, the cardia (particularly in the presence of axial hiatal hernia), the distal duodenal bulbs, and the rectosigmoid junction. In addition, rare diverticula such as Zenker's diverticulum, or duodenal diverticula, as well as esophageal, gastric, or intestinal stenosis, puts the patient at increased risk of perforation and should be ruled out by EGD prior to EUS in all patients.

Intestinal stenoses that cannot be passed by echoendoscopes are to be expected in up to 25% of patients presenting with esophageal and rectal carcinomas, while this problem only rarely occurs in gastric and pancreatic carcinoma. The German EUS register (see above) reported only ten cases with GI perforations out of 14,000 diagnostic patient cases (0.07%). Of these, six occurred in the duodenum, two in the esophagus/hypopharynx, one in the stomach, and one in the rectum (Gottschalk et al. 2012). Risk factors for perforations include low level of investigator's experience, unexpected intestinal stenoses, and the presence of diverticula (Polkowski et al. 2012; Wang et al. 2011; Gottschalk et al. 2012).

The number of GI perforations does not appear to be significantly increased by EUS-FNMA techniques, though some cases with free air in the peritoneal cavity after EUS-FNA have been reported. According to these reports, the majority of patients did not exhibit clinical complaints or longer-lasting pain or fever. In contrast, EUS-guided therapy carries a significant risk of GI perforation in most instances and depends on investigator experience as well as on the particular therapeutic maneuver used (see following chapter).

Septicemia and peritonitis are extremely rare incidents after EUS-FNA, if caused by this procedure at all. However, when EUS-FNA of cystic lesions (including pseudocysts, neoplastic cysts, ascites) is considered, peri-interventional antibiotic therapy should be an integral part of the standard operating procedure, since EUS-FNA of cystic and infected lesions exposes the patients to a significantly greater risk of procedure-borne infectious complications.

EUS-FNA of mediastinal cysts can eventually lead to catastrophic events such as mediastinitis and death, without adding any substantial diagnostic or therapeutic yield for such patients. In consequence, its use for bronchogenic cysts and esophageal duplication cysts is not indicated and should be avoided in all cases (Jenssen et al. 2011b). If in doubt, apply intravenous contrast material (SonoVue, Bracco) to rule out neoplastic cysts in cases in whom cellular detritus suggests solid appearances within mediastinal cystic lesions.

If unexpected and/or suspicious cystic lesions are found during in other organs or compartments than the mediastinum during upper GI EUS procedures, we recommend application of i.v. antibiotics prior to FNA of such lesions. Typical antibiotics include broad-spectrum penicillins (such as ampicillin or piperacillin) or gyrase inhibitors such as ciprofloxacin (200 mg). Administration of antibiotic therapy should then be continued until the following day. In immunocompromised patients, antibiotics should be administered generously at the discretion of the treating physician.

For transrectal EUS-FNP, general prophylaxis with antibiotics is not required but should be tailored to individual risk of patients.

Severe hemorrhages after diagnostic EUS-FNA are only rarely encountered. Typical risk factors for major bleedings include severe coagulopathies, anticoagulants (including NOAK), and portal hypertension. Very few fatalities, however, have been reported in the literature. In contrast, continued treatment with aspirin (ASS) appears to be safe and is generally not associated with increased rates of severe hemorrhage after diagnostic EUS-FNA. Continued treatment with combinations of ASS with clopidogrel or similar substances, however, should be avoided prior to EUS-FNA, since this combination increases the risk of severe and prolonged hemorrhage (Polkowski et al. 2012; Jenssen et al. 2011b). Figure 5.6 depicts a typical post-FNA bleeding that was visible during EUS-FNA; in this case, no clinical symptoms occurred, and no consequences had to be considered.

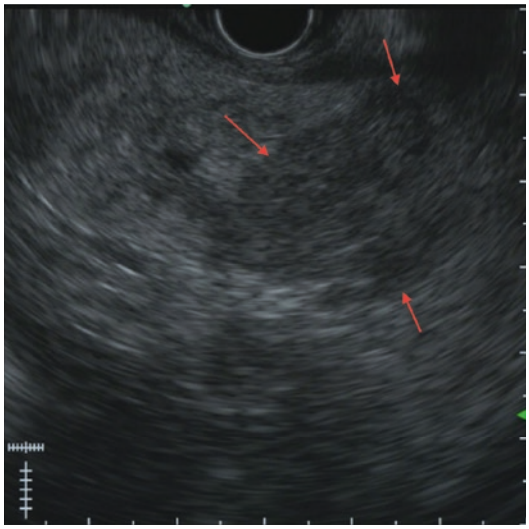

Fig. 5.6 Localized bleeding after EUS-FNP at the pancreatic head. The asymptomatic bleeding stopped without intervention

5.2 EUS-Guided Drainage Techniques

5.2.1 EUS-Guided Cyst Drainage

Initially, bulging of the GI wall was a prerequisite for endoscopic cyst drainage (Bahari and Ismail 1982). By introduction of endoscopic ultrasound as access guidance, intervening vessels within the puncture tract could be avoided (Giovannini et al. 1998). Additionally, fluid collections without bulging became safely accessible (Park et al. 2009;

Varadarajulu et al. 2008). Even without randomized controlled studies, guidance by EUS became the method of choice for access.

Initially, the cyst is punctured by the use of a 19G needle, which makes it possible – after diagnostic aspiration of cyst fluid – to proceed with the introduction of a 0.035″ guide-wire. This guidewire serves as the track for further bougienage and dilatation with instruments such as cystostoms and balloon catheters. The widened access is secured by one or more drainages. Double-pigtail drainages have the advantage of being stable in position. Increasingly, metal stents are used for this purpose.

Alternatively, all-in-one sets are increasingly used, including instruments for access, dilatation, and drainage via a metal stent designed for application via the working channel of the echoendoscope. For further details, see ► Chap. 10.

5.2.2 EUS-Guided Retroperitoneal Necrosectomy

Endoscopic therapy of infected pancreatic necrosis was described in 2000 by Seifert (Seifert et al. 2000). The access to the necrotic cavity is gained analogously to EUS cyst drainage. In contrast, the final diameter should be wider to allow the removal of necrotic material. The location of the access is crucial, since necrosectomy in inversion can be extremely difficult of even impossible.

The indication for endoscopic necrosectomy has to be questioned critically, since it has been shown that even proven infected necrosis can be managed conservatively in many cases (Runzi et al. 2005). In general, only a symptomatic necrosis could be an indication for an intervention. Symptoms could be evoked either by septic complications or by the size of the lesion compressing adjacent structures. Laboratory findings (such as elevation of CRP or leukocytosis) or fever could be indicative for an infection. However, infectious complications have to be taken into account after the beginning of the third week of the pancreatitis, while beforehand, the same findings could be a part of a systemic inflammatory response syndrome (SIRS). The size of a necrosis could lead to an obstruction of the gastrointestinal tract or of the bile duct, while in others, it is asymptomatic or accompanied by pain.

After providing the indication, several therapeutic options have to be weighed. Apart from an endoscopic procedure, surgery and percutaneous drainage are options. These modalities are not exclusive; they could be combined with each other. By percutaneous drainage, a rapid decompression of infected areas is feasible, which often leads to an impressive stabilization of the patient. By guidance of percutaneous ultrasound or computed tomography, it is available in every hospital und even for patients in a dismal condition. The external drainage could serve as flushing access when combined with an internal endoscopic drainage. However, the removal of necrosis by a sole percutaneous access is only feasible with large-bore catheters in combination with long-term flushing. Additionally, this method is associated with a high risk of a persisting pancreatic fistula.

Open surgical removal of infected necrosis, for years the gold standard of therapy, is associated with high mortality. Despite optimization of the surgical technique including minimal invasive retroperitoneal access, the mortality seems to stay higher than endoscopic necrosectomy as described below.

Surgery can be necessary if endoscopic expertise is not available locally and the patient cannot be referred to another hospital. In rare cases, necrosis could be out of range for an endoscopic intervention.

Access to the necrotic cavity is obtained in the same manner as for endoscopic cyst drainage. A suitable drainage site does not show any interfering vessels. An area is preferred as the puncture site where there is an inflammatory connection between the cyst wall and the gastrointestinal wall. In this case, the muscularis propria and the cyst wall may not be delineated. A transgastric route is easier and therefore preferred, since the transduodenal access could be angulated and tight. The less elevation is needed for forward puncturing, the greater is the force. Therefore, a necrotic cavity should be addressed at the end, which is next to the cardia.

When using the sequential technique, the first step is puncturing with a 19 G EUS needle (◘ Fig. 5.7). Aspirated fluid is used for microbiological and laboratory examinations. Instead of the EUS standard fine needle, a specially designed access needle with a sharp stylet at the tip could be used, which becomes blunt after removal of this stylet. The next step is securing the access by introduction of a 0.035″ guide-wire into the necrotic cavity including several loops. (◘ Fig. 5.8). The position of the guide-wire could

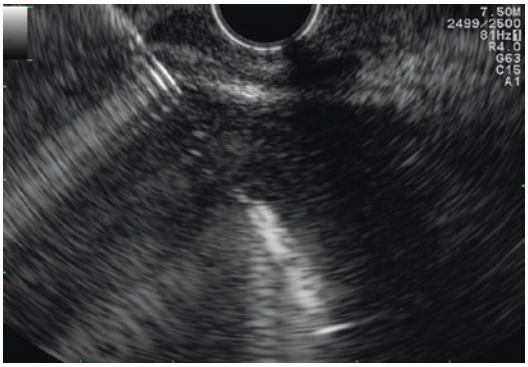

Fig. 5.7 EUS image of the puncture of a pancreatic pseudocyst. The cyst is punctured from *left above*. The reflex of the needle may be easily seen

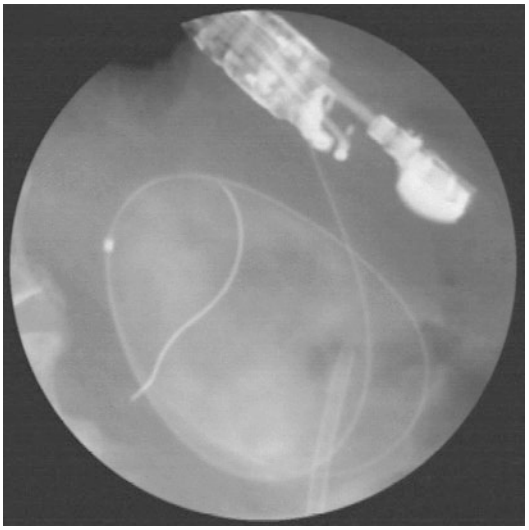

Fig. 5.8 Fluoroscopic image after endosonographic puncture of a pseudocyst, contrast injection, and insertion of the guide-wire with several backup loops

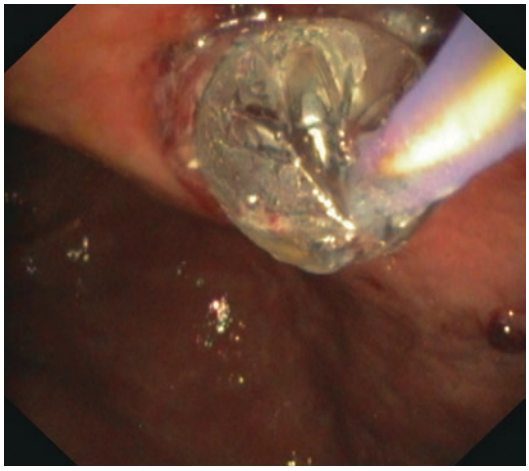

Fig. 5.9 Endoscopic image of an insufflated dilation balloon, which should widen the access to a necrotic cavity

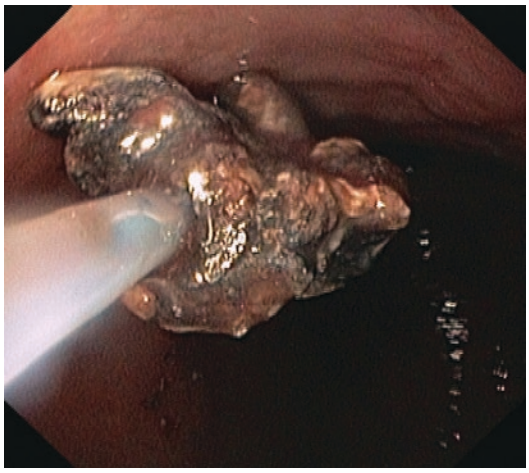

Fig. 5.10 Endoscopic image: necroses are removed by a polyp grasper

be controlled either by endoscopic ultrasound or by fluoroscopy.

The next step is expansion of the access channel electrically by cystostome or mechanically by balloon dilation (Fig. 5.9). The diameter needed for endoscopic necrosectomy is in the range of 16–20 mm. In the case of inflammatory adherence, this diameter could be achieved during the first session, while in other patients a stepwise dilation is recommended. After initial placement of a single 10F drainage, it is feasible to achieve the needed diameter by stepwise adding several drainages. The peri-stent inflammatory reaction leads to the establishment of a stable channel for further removal of necrosis.

Alternatively, the access could be established by lumen-apposing metal stents, which make a faster procedure possible. The costs of this specially designed stent are high but may be justified by the benefits of less and shorter interventions.

At least after the second intervention, the channel is stable and endoscopic necrosectomy can be performed safely (Jurgensen et al. 2012). To begin even during the first session could be associated with an increased risk of perforation, as seen in the American multicenter study (Gardner et al. 2011).

Polyp graspers, snares, and baskets are used to remove necrosis (Fig. 5.10). However, all instruments have their limitations when used to grasp

the necrosis of either smooth or bezoar-like consistence. As a result, the removal of necrosis is enormously time-consuming. In our experience, three endoscopic sessions each lasting 2 h is typical just for removal (Jurgensen et al. 2012). The necrosis is grasped in its cavity and then dropped in the gastrointestinal tract. By this removal, the cavity can become smaller. After each intervention, drainages are repositioned in the channel to prevent a premature closure with the risk of retention of infectious remnants.

Finally, all transluminal drainages are removed 6–8 weeks later, with intermediate demission of the patient. Usually, the cavity has closed in the meantime with the drainages as the last remnant.

Initially successful in single patients, the efficacy of this method has been confirmed in the meantime by three multicenter studies (Gardner et al. 2011; Seifert et al. 2009; Yasuda et al. 2013). Mortality was in the range of 6–8%. One little randomized study was able to show clear advantages for endoscopic necrosectomy in terms of inflammatory parameters compared to a surgical approach (Bakker et al. 2012). However, the difference of mortality (four in the surgical group versus one death in the endoscopic group, with ten patients in each therapeutic arm) was not significant. A randomized comparison from the Dutch pancreatis group is awaited.

In conclusion, endoscopic necrosectomy – if available – has become the method of choice for symptomatic pancreatic necrosis. However, it does not solve all problems, and consensus to its use should be achieved in interdisciplinary consensus.

5.2.3 EUS-Guided Therapy of Common Bile Duct and Pancreatic Duct

EUS-Guided Cholangiodrainage

EUS-guided drainage in cases of cholestasis has been increasingly used over recent years in expert centers. However, it still cannot be judged as an established method. Two different approaches may be distinguished: EUS-guided guide-wire insertion as the basis for a rendezvous maneuver, and EUS-guided direct drainage of bile ducts. A mechanical cholestasis, untreatable by a less invasive method, is an indication for both approaches. This constellation could be given in a patient with inoperable pancreatic carcinoma, when the papilla cannot be accessed or cannulated and the patient refuses to have a percutaneous transhepatic drainage.

The initial step is to puncture the enlarged intrahepatic bile ducts of the dilated common bile duct with a 19G EUS needle under EUS guidance. Injection of contrast and visualization of the bile duct by fluoroscopy is the next. Both are easy steps for an experienced endosonographer. Cholangiography is successful in nearly every patient (97–100%) (Isayama et al. 2013). Then, a 0.035″ guide-wire is advanced through the needle. The attempt is to advance its antegrade through the papilla. If this is successful, the guide-wire can be picked up at the papilla and be used for retrograde intubation, as part of a classical rendezvous maneuver. Further procedure is as known from conventional ERC.

However, even specialists fail in one of four patients to pass the guide-wire antegradely through the papilla (Isayama et al. 2013; Will and Meyer 2012). Now, the concept has to be switched to EUS-guided cholangiodrainage. To stop after puncturing, a congested bile duct with a 19G needle without drainage can become disastrous due to development of a bile fistula into the retroperitoneum. This direct drainage is a more challenging technique and requires a huge amount of technical skill from the endoscopist: after puncturing and advancing a guide-wire, the access has to be enlarged for introduction of a stent. This transduodenal access is characterized by a pushed endoscope position and a contorted route for the further drainage. Additionally, no inflammatory adhesions between common bile duct and the duodenal wall prevent the stiff bile duct from evasion. In case of failure, bile leaks into the retroperitoneum.

If choosing a transhepatic route (◘ Fig. 5.11) the forward power could be limited, resulting in difficulties in widening the access and protruding the drainage. Both access routes include the risk of drainage dislocation, with potentially disastrous consequences.

Fully covert stents (i.e., Axios stent ©) with smaller calibers suitable for the bile duct are developed recently for EUS-guided application.

EUS-Guided Pancreatic Duct Drain age

As for cholestasis, EUS-guided drainage of the pancreatic duct is an attractive option in case of a congested duct. The rare clinical situations of

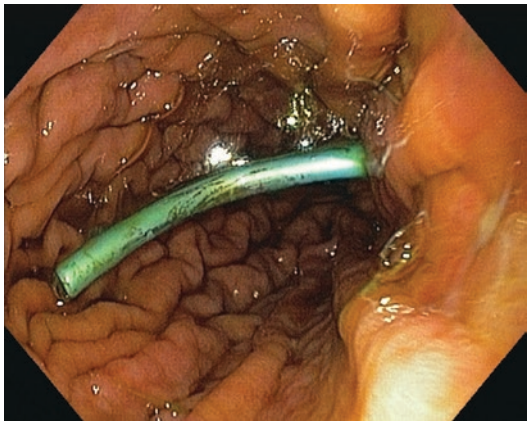

Fig. 5.11 Endoscopic image of a transgastric bile drainage located to drain a dilated left hepatic bile duct

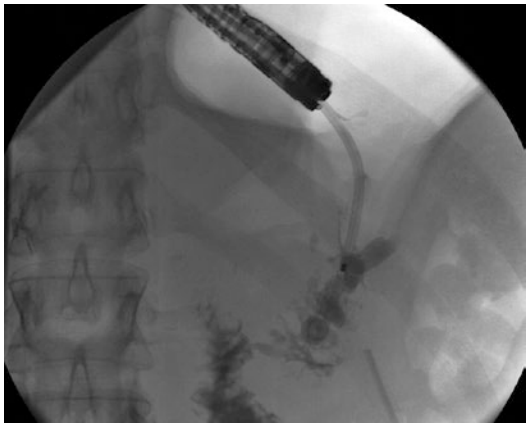

Fig. 5.12 X-ray of a transgastric pancreatic duct drainage after pancreatic head resection. The patient became symptomatic secondary to a stenosis of her filiform pancreatic anastomosis

an intraductal infection or pain caused by inhibited pancreatic outflow are good indications. In most patients, a transpapillary access is feasible. Additionally, surgery is an alternative therapeutic option with better long-term results compared to endoscopy. When considering an EUS-guided pancreatic duct drainage, the technical difficulty and the missing long-term concepts for further management of transmural drainages have to be taken into account.

In most patients, the pancreatic duct is punctured transgastrically. The technique is similar to the above-described procedure of cholangiodrainage. If the transpapillary access fails, the pancreatic parenchyma is often stiff due to chronic pancreatitis. Additionally, the unfavorable further route of the duct is problematic. Finally, if first drainage is successful (Fig. 5.12), these drainages often migrate spontaneously. As a result, only in a small number of interventions it is possible to perform pancreatic duct drainage with an acceptable success rate (Will et al. 2007).

5.2.4 EUS-Guided Local Tumor Therapy

Endoscopic ultrasound is a local method and is therefore only able to be an instrument of local therapy. Therefore, it can be a curative option only for nonmetastatic tumors, which have to be addressed due to their prognosis or due to their symptoms (for instance resulting from hormone secretion). Additionally, it could reduce locally the tumor mass as part of a multimodality treatment (debulking). Finally, endosonography is able to place fiducial markers to guide further radiation therapy.

After the first report of an ablation of an insulinoma by alcohol (Jurgensen et al. 2006), this successful local therapy of hormone-secreting tumors has been confirmed by many case reports and small case series. Additionally, alcohol lavage or injection of paclitaxel has been described for cystic pancreatic tumors. In some of them, it was possible to achieve complete remission by this therapy (DeWitt et al. 2010). However, this therapeutic approach is under discussion, since the exact nature of the cystic lesions and the long-term follow-up were not clarified.

The therapy of a single hepatocellular carcinoma by EUS-guided alcohol injection or by laser ablation has been described.

The feasibility of local therapy by EUS-guided cryoprobe or by injection of modified virus has been evaluated in humans. Long-term follow-up data are not provided. The EUS-guided placement of fiducial markers to direct radiation therapy is feasible in patients with pancreatic or prostate carcinoma. The EUS-guided application of radioactive seeds is feasible. Long-term data is missing as well.

In conclusion, EUS-guided tumor therapy is still experimental. Outside of studies, it could be considered in patients with neuroendocrine tumors or hepatocellular carcinomas, if surgery is not feasible.

5.2.5 EUS-Guided Therapy: Miscellaneous (Fistulae, Vessels)

Endoscopic ultrasound offers the option of further interventions, which are not sufficiently evaluated yet and therefore should not be discussed in detail. Fistulas of the pancreas could develop after pancreatic surgery or as part of severe pancreatitis. These fistulas are often asymptomatic, if they drain into the gastrointestinal tract. In contrast, they could be symptomatic, if they drain into the pleural cavity or cutaneously. Often they are located next to the stomach and could be punctured and filled with contrast by use of the technique described above for pancreatic cysts and necroses. Even if small in diameter, they could be cannulated by a guide-wire and drained transgastrically after dilatation. Additionally, an attempt should be made to improve the transpapillary outflow.

EUS-guided thrombin injection into visceral aneurysms in humans and the obliteration of submucosal arterial vessels in animals have been described. The application of this technique for venous vessels is mainly restricted to varices, mostly of the fundus. Occlusion is achieved by injection of cyanoacrylate or of small coils into the feeding vessels. However, endosonography is often not available in case of acute fundal variceal bleeding, while an obliteration therapy – either endoscopically or via EUS – is not established as part of secondary prophylaxis.

5.3 EUS-Guided Celiac Plexus Neurolysis (EUS-CPN)

■ Introduction, Background, and Indications for EUS-CPN

Pancreatic carcinomas and retroperitoneal metastasis of other tumors frequently produce massive, long-lasting, intractable pain in affected patients. This pain may be difficult to control and manage solely by orally administered drugs or patches (American Cancer Society: Cancer Facts and Figures 2007). Optimizing pain management is therefore the most important goal of palliative care in such patients. In addition, opiates and morphine frequently exhibit various disabling side effects ranging from severe constipation to dizziness/vertigo/nausea and vomiting which may significantly limit or hamper their dosage and use in this patient group.

The celiac plexus is located just below the diaphragm at level of the first lumbar spine (LSP-1). It consists of a dense network of sympathetic nerve fibers that run parallel to the ventral aspect of the abdominal aorta at level of the root of the celiac trunk.

The celiac plexus transmits pain signals of almost all visceral organs cephalad including pancreatic, biliary, hepatic, renal, intestinal, and pelvic pain to higher CBS centers. It is, however, connected with other ganglionic networks. The celiac plexus apparatus is not the sole source of pain in such tumors, since other connected neural structures are also involved in visceral pain generation and transmission, including the hypogastric and mesenteric plexus. Therefore, celiac plexus neurolysis alone may always be limited by this anatomic reality.

Local treatment of chronic pain syndromes by celiac plexus injection has been attempted for decades, particularly in patients with pancreatic carcinoma and chronic pancreatitis. Single centers developed the first percutaneous treatment plans for CPN back in the 1950s, but these techniques never made it far due to great limitations of X-ray techniques until CT scanning was developed in the 1980s of the last century. After CT scanning became common, several centers tried ventral or dorsal access routes under CT guidance to reach the celiac plexus region percutaneously under real-time conditions. The first uncontrolled studies and case series showed some limited clinical success in selected cases that were reported to range up to 60–70% of patients included. However, due to the high degree of specialization and experience, only a few centers offered this form of treatment, and some cases were reported that developed serious adverse events – including paraplegia, severe hemorrhages, infections/abscess formation, ischemia, and even death.

During the 1990s, the novel EUS technique facilitated further refinement and new developments for EUS-guided CPN under real-time conditions. First case reports and case series (Romanelli et al. 1993; Mercadante and Nicosia 1998) and subsequent uncontrolled clinical stud-

ies suggested (Wiersema and Wiersema 1996; Puli et al. 2009; Arcidiacono et al. 2011) some positive and lasting effects of EUS-CPN in selected patients. These effects included reduction of analgesics (dose, number of pills taken) and transient pain relief in up to 80–90% of treated patients for a couple of weeks (Mercadante and Nicosia 1998). The complication rate reported was low, and most adverse events consisted only of mild events including transient diarrhea, transient hypotension, or light pain with spontaneous relief.

One of the most intriguing problems with this EUS-treatment technique is the fact that the simple anterior plexus injection of ablative substances cannot be effectively targeted and visualized during the procedure. Due to the lack of visibility using EUS-FNI, it is not possible to calculate, or assess, the number of plexus fibers/ganglia during intervention, which limits its applicability in clinical practice substantially. Up to now, no sham-controlled, prospective, randomized clinical study exists to serve as an evidence base for EUS-CPN.

Some working groups have, therefore, studied effects of bilateral plexus injections in one single session, or in some patients, EUS-guided «broad-range» injections using small-caliber 25-gauge needles that included areas around the root of the superior mesenteric artery (SMA). These studies reported some improvement, but confirming data are still lacking. Clinical studies are also difficult to achieve since modern analgesics offer subtle and detailed treatment opportunities for most affected patients, and many patients are also subject to oncologic or radio-oncologic treatment.

■ Celiac Plexus Blockade and CP Neurolysis (EUS-CPB, EUS-CPN)

Celiac plexus blockade (CPB) denotes an EUS-guided injection technique for the local therapy of chronic pancreatic pain syndromes. EUS-CPB is performed by topical injection of drugs to block celiac nerve ganglia without permanent destruction of ganglionic neuronal tissues. This approach can readily be compared with anesthesiological nerve block techniques in different clinical scenarios. The goals of EUS-CPB are blockade of neuronal pain transmission signals cephalad to the connected pain networks by using reversible substances such as local anesthetics (i.e., lidocaine or procaine), with or without adding local steroids (triamcinolone) to reduce perineural inflammation in such circumstances.

In contrast, celiac plexus neurolysis (EUS-CPN) causes permanent and irreversible nerve damage and thus toxically destroys most tissues that are hit by the injection jet during CPN. For this purpose, a pure 98% ethanol solution – combined with a common local anesthetic – has been used in most instances.

To avoid toxic hazards during EUS-CPN, both operator and assistant(s) are required to wear fluid-resistant coats and face masks during the operation to protect against toxic splashes, eye contacts, and other harmful collateral effects. For the performance of EUS-CPN, different injection needles have been used ranging from small-caliber 25-G needles over 22-G FNA needles up to 19-G therapeutic FNA needles, while one dedicated injection needle with multiple side holes is still commercially available (companies: MediGlobe, Cook, Boston Scientific, MTW, Olympus, Covidien, and others). Up to now, no clinical study exists that clearly demonstrates distinct differences in terms of the therapeutic yield of the dedicated injection needle that would justify its very high price. Personally, we recommend use of 19- or 20-gauge FNA needles for EUS-CPN, since the wide lumen offers some advantages for the technical performance of injections – even in relatively rigid tissues. This approach should also – at least theoretically – reduce the risk of toxic splashing under such therapeutic conditions.

For EUS-CPN, a dedicated linear sideways-looking or forward-looking echoendoscope is to be used that allows for direct visualization of the root of the celiac plexus and also depicts some of the plexus ganglia in many cases (see paragraph below). The celiac plexus originates ventrally and cephalad of the proximal abdominal aorta, while the celiac plexus and its surrounding ganglion network is largely located in direct anatomical proximity of such visible nerve ganglionic nodules. The smaller nerve fibers and networks, however, cannot be visualized by EUS which limits the technique to some visible – and many suspected but invisible – structures in this clinical setting (see cartoon/image in ◘ Fig. 5.13a). The basic materials and instruments for the performance of EUS-CPN are demonstrated by ◘ Fig. 5.13b.

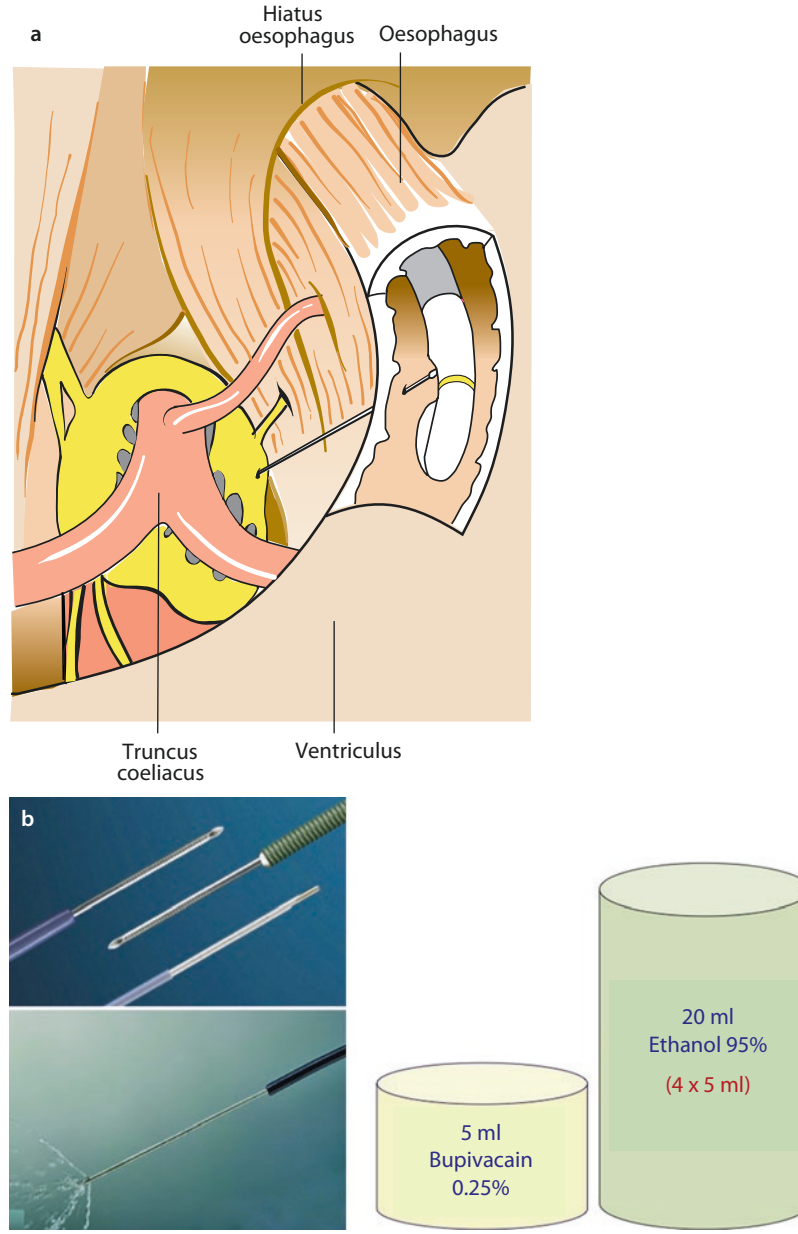

Fig. 5.13 **a** Anatomical position (sketch drawing) of the celiac plexus. **b** Additional materials for the EUS-guided plexus neurolysis of the celiac plexus, also referred to as «EUS-guided celiac injection therapy» (EUS-FNI)

Prior to EUS-CPN, the echoendoscope is forwarded and positioned in the proximal stomach immediately below the gastroesophageal junction. Under direct EUS visualization, the needle is then carefully advanced through the stomach wall and forwarded to the visible celiac plexus ganglia, or the region to where these structures are suspected. The principles of this common EUS-CPN are schematically demonstrated in Figs. 5.14a and b. After advancing the needle toward its target structures, direct injection of a long-lasting local anesthetic agent should be performed at first, for instance, by injecting 5–15 cc of bupivacaine 0.25% (or a similar agent) on both sides of the celiac root – if possible to avoid procedure-induced pain.

Based on our own experience, we believe that a dose of 20 ml is usually sufficient.

Bilateral EUS-CPN and Direct Plexus Neurolysis by Intra-ganglionic Application

According to present studies (Hollerbach 2013; LeBlanc et al. 2011; Ascunce et al. 2011; Wyse et al. 2011), there seems to be no significant difference

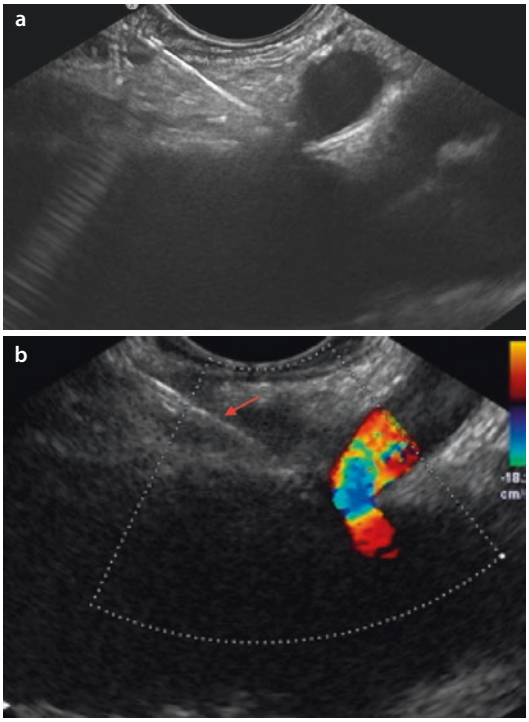

Fig. 5.14 **a** Position of EUS-transducer immediately distal and cephalad of the posterior diaphragm and view on the celiac trunk root; the FNA needle has been pushed out until its tip almost reaches the origin of the celiac trunk. **b** Duplex EUS shows the exact position of the perfused truncus artery that needs to be avoided during FNI; the needle tip reaches an echo-reduced nodular structure in this area that refers to parts of the celiac plexus nerve network in this region

between solitary injections ventrally and cephalad of the celiac trunk and bilateral injection therapy on both sides of the celiac trunk. For reasons of safety we therefore support ventral access to the root of the celiac trunk for topical ethanol injection to facilitate plexus neurolysis in patients, particularly when the visibility of the needle is obscured before, or during injection therapy. One recent randomized controlled study compared the central injection approach with bilateral injection techniques but found no significant differences in terms of clinical outcome. Some other uncontrolled smaller studies, however, have reported some benefit with the bilateral injection approach, but the clinical outcome difference of these findings remains unclear.

Using modern high-resolution EUS equipment, some of the major celiac plexus ganglia can be directly visualized in many patients. Usually, the plexus ganglia can be depicted as a chain of echo-reduced small nodules ventrally

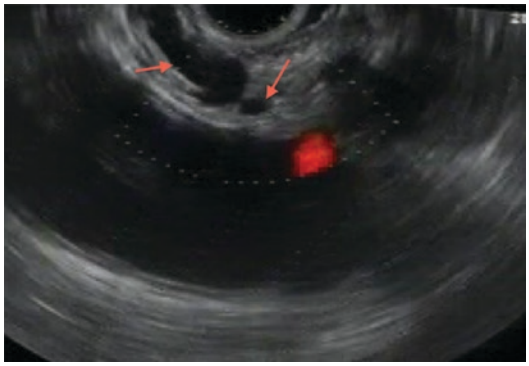

Fig. 5.15 EUS depiction of several nodular nerve structures of the celiac plexus network close to the root of the celiac trunk

and left of the celiac trunk but can easily be misinterpreted as lymph nodes or aspects of the left adrenal gland (Fig. 5.15). Compared with lymph nodes, however, celiac ganglia do not exhibit central echo-enhanced reflexes and are usually multiple and band-like in shape while mimicking a chain of pearls in many cases. Celiac ganglia are supposed to be clearly visible in approximately 70–80% of patients, but this visibility can be greatly obscured by factors such as presence of ascites, retroperitoneal carcinosis, and others. One recent retrospective, uncontrolled study assessed the feasibility and outcome of direct intra-ganglionic administration of ethanol for EUS-CPN and compared this technique with bilateral ethanol injections. Results suggest that direct EUS-CPN into celiac ganglia may result in significantly ameliorated pain scores of patients after CPN, with improvement of VAS scores in 68% of patients versus 33% of patients in the bilateral injection group. This study, however, is mainly limited due to its uncontrolled design, heterogeneity, and possible patient bias. Figure 5.16 demonstrates the CT image of the distribution of ethanol fluid mixed with contrast fluids at the celiac plexus base upon EUS injection (upper panel, unilateral injection; lower panel, bilateral injection). EUS-CPN can be performed both during diagnostic tumor staging and biopsy (endosonographic «one-stop shopping») or as separate local therapy approach.

Other studies have been performed that aimed at pain reduction by topical injection of ethanol and/or steroids (usually triamcinolone) in benign pancreatic diseases such as advanced chronic

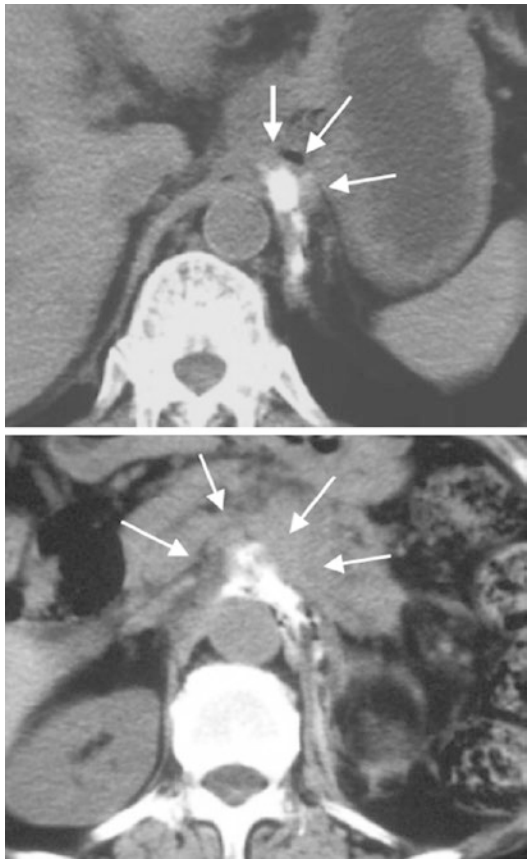

Fig. 5.16 Distribution of fluids upon injection of absolute alcohol mixed with fluoroscopic contrast agents around the base of the celiac trunk and the celiac plexus ganglia after EUS-FNI: the CT scans show the typical distribution of fluids after **a** unilateral injection and, **b** after bilateral injection

pancreatitis, a term called *celiac plexus block* (EUS-CPB). However, results of these uncontrolled and usually retrospective trials (Kaufman et al. 2010; Wilcox 2012) did not point toward clinically meaningful and convincing results since short-term «success rates» reported did usually not exceed 50% of patients, if being successful at all. Up to now, no controlled, randomized studies with regard to this technique exist; there are no long-term experiences, and patient selection seems to be heterogeneous in all previous studies. Hence, there is still no evidence-based justification for EUS-CPB with steroids in this setting, while on the other hand, some reports have been published that reported serious adverse events in some treated patients, including local abscess formation and septicemic episodes and including some lethal patient cases due to ischemic necrosis of stomach and bowel wall (Fujii et al. 2012; Loeve and Mortensen 2013) – the latter only occurring in combination with ethanol application. In summary, whenever EUS-CPB is considered for local pain therapy in chronic pancreatitis, this approach should only be performed in vigorously controlled clinical studies.

Contraindications for Celiac Plexus Neurolysis

On the basis of previous and current studies, EUS-CPN is considered to be a relatively safe therapeutic intervention. However, some peculiar situations exist that should be considered as «red flags» – or absolute and relative contraindications – for any therapeutic intervention around the celiac plexus:

- Lack of signed informed consent of the patient (absolute)
- Intervening vessels within the needle tract that cannot be avoided, e.g., in portal hypertension (relative)
- Lack of visibility of needle tip during the procedure (absolute)
- Severe coagulopathies (INR >3, thrombocytopenia <50,000): absolute
- Need for continued antiplatelet medication or anticoagulants such as NOACs, clopidogrel + aspirin, coumarone, warfarin, and others (relative)

The number and outcome of severe adverse events (SAEs) – or side effects – during EUS-CPN has been shown to be relatively low; however, this procedure may significantly harm some patients at risk, including fatal outcome, thus disclosing a small albeit significant mortality rate. The overall number of AEs with EUS-CPN may lie somewhere in the range between 5% and 10% of procedures, including at least two fatal cases dying from ischemic necrosis of the spleen and/or small intestine. Hence, the indication for EUS-CPN and the conduct of this procedure should always be carried out with the utmost care and thoroughness till the end of the intervention in every patient case to prevent such disastrous outcomes.

Typical expectable complications (Puli et al. 2009; Arcidiacono et al. 2011; Hollerbach 2013; Fujii et al. 2012; Loeve and Mortensen 2013) include:

- Hypotension, usually self-limited
- Transient diarrhea (1–2 days)
- Local hemorrhage (usually self-limited, conservative treatment)

- Fever/hyperthermia, self-limited
- Local infection/abscess formation/septicemia: reported only after steroid injections
- *Rarely*: ischemic infarction (stomach, spleen, small intestine, colon – single cases)
- *Rarely*: spinal infarction/transient neurologic deficits (palsy)

References

Adler G, Seufferlein T, Bischoff SC, Brambs HJ, Feuerbach S, Grabenbauer G, Hahn S, Heinemann V, Hohenberger W, Langrehr JM, Lutz MP, Micke O, Neuhaus H, Neuhaus P, Oettle H, Schlag PM, Schmid R, Schmiegel W, Schlottmann K, Werner J, Wiedenmann B, Kopp I. S3-Guidelines «Exocrine pancreatic cancer» 2007. Z Gastroenterol. 2007;45:487–523.

American Cancer Society: Cancer Facts and Figures. Am Cancer Soc, Atlanta: 2007.

Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev. 2011;3:CD007519.

Ascunce G, Ribeiro A, Reis I, Rocha-Lima C, Sleeman D, Merchan J, Levi J. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). Gastrointest Endosc. 2011;73(2):267–74.

Bahari HM, Ismail A. Endoscopic transgastric drainage of pseudopancreatic cyst. Med J Malaysia. 1982;37:316–7.

Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307:1053–61.

DeWitt J, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. Gastrointest Endosc. 2010;72:862–6.

Dumonceau JM, Polkowski M, Larghi A, Vilmann P, Giovannini M, Frossard JL, Heresbach D, Pujol B, Fernandez-Esparrach G, Vazquez-Sequeiros E, Gines A. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2011;43:897–912.

Fujii L, Clain JE, Morris JM, Levy MJ. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E265–6. Epub 2012 Jul 13

Gardner TB, Coelho-Prabhu N, Gordon SR, Gelrud A, Maple JT, Papachristou GI, Freeman ML, Topazian MD, Attam R, Mackenzie TA, Baron TH. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718–26.

Giovannini M, Bernardini D, Seitz JF. Cystogastrotomy entirely performed under endosonography guidance for pancreatic pseudocyst: results in six patients. Gastrointest Endosc. 1998;48:200–3.

Gottschalk U, Jenssen C, Webhofer T, Düffelmeyer M. How dangerous is endoscopic ultrasound? Results of a German prospective multicentric endoscopic ultrasound registry. Endoscopy. 2012;44:1231. submitted

Hollerbach S. Endosonografisch gesteuerte Plexus-coeliacus-Blockade (EUS-FNI). In: Jenssen C, et al., editors. Kursbuch Endosonografie. Stuttgart: Thieme-Verlag; 2013.

Hollerbach S, Willert J, Topalidis T, Reiser M, Schmiegel W. Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. Endoscopy. 2003;35:743–9.

Hollerbach S, Böcking A, Wellmann A. Interventionelle Endosonographie. Sichere Tumordiagnosen sind auch ohne Staging-Operationen möglich. Dtsch Arztebl. 2010;107:A2390–1.

Isayama H, Nakai Y, Kawakubo K, Kawakami H, Itoi T, Yamamoto N, Kogure H, Koike K. The endoscopic ultrasonography-guided rendezvous technique for biliary cannulation: a technical review. J Hepatobiliary Pancreat Sci. 2013;20:413–20.

Jenssen C, Dietrich CF. Endoscopic ultrasound of gastrointestinal subepithelial lesions. Ultraschall Med. 2008;29:236–56. quiz 257-64

Jenssen C, Hollerbach S. Endosonografisch geführte Feinnadelpunktion (EUS-FNP) In: Kursbuch Endosonografie. Stuttgart: THIEME Verlag; 2013.

Jenssen C, Möller K, Sarbia M, Wagner S. Endoscopic ultrasound-guided biopsy — indications, problems, pitfalls, troubleshooting, clinical impact. In: Dietrich CF, editor. Endoscopic ultrasound. An introductory manual and atlas. Stuttgart/New York: Thieme; 2011a.

Jenssen C, Mayr M, Nuernberg D, Faiss S. Complications of endoscopic ultrasound: risk assessment and prevention. In: Dietrich CF, editor. Endoscopic ultrasound. An introductory manual and atlas. Stuttgart/New York: Thieme; 2011b. p. 176–96.

Jurgensen C, Schuppan D, Neser F, Ernstberger J, Junghans U, Stolzel U. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006;63:1059–62.

Jurgensen C, Neser F, Boese-Landgraf J, Schuppan D, Stolzel U, Fritscher-Ravens A. Endoscopic ultrasound-guided endoscopic necrosectomy of the pancreas: is irrigation necessary? Surg Endosc. 2012;26:1359–63.

Kaufman M, Singh G, Das S, Concha-Parra R, Erber J, Micames C, Gress F. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol. 2010;44(2):127–34.

LeBlanc JK, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, Johnson C, Howard TJ, Lillemoe KD, DeWitt J. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two ? Gastrointest Endosc. 2011;74(6):1300–7.

Levy MJ, Gleeson FC, Campion MB, Caudill JL, Clain JE, Halling K, Rajan E, Topazian MD, Wang KK, Wiersema

MJ, Clayton A. Prospective cytological assessment of gastrointestinal luminal fluid acquired during EUS: a potential source of false-positive FNA and needle tract seeding. Am J Gastroenterol. 2010;105:1311–8.

Loeve US, Mortensen MB. Lethal necrosis and perforation of the stomach and the aorta after multiple EUS-guided celiac plexus neurolysis procedures in a patient with chronic pancreatitis. Gastrointest Endosc. 2013;77:151.

Mercadante S, Nicosia F. Celiac plexus block: a reappraisal. Reg Anesth Pain Med. 1998;23:524.

Moehler M, Al-Batran SE, Andus T, Anthuber M, Arends J, Arnold D, Aust D, Baier P, Baretton G, Bernhardt J, Boeing H, Bohle E, Bokemeyer C, Bornschein J, Budach W, Burmester E, Caca K, Diemer WA, Dietrich CF, Ebert M, Eickhoff A, Ell C, Fahlke J, Feussner H, Fietkau R, Fischbach W, Fleig W, Flentje M, Gabbert HE, Galle PR, Geissler M, Gockel I, Graeven U, Grenacher L, Gross S, Hartmann JT, Heike M, Heinemann V, Herbst B, Herrmann T, Hocht S, Hofheinz RD, Hofler H, Hohler T, Holscher AH, Horneber M, Hubner J, Izbicki JR, Jakobs R, Jenssen C, Kanzler S, Keller M, Kiesslich R, Klautke G, Korber J, Krause BJ, Kuhn C, Kullmann F, Lang H, Link H, Lordick F, Ludwig K, Lutz M, Mahlberg R, Malfertheiner P, Merkel S, Messmann H, Meyer HJ, Monig S, Piso P, Pistorius S, Porschen R, Rabenstein T, Reichardt P, Ridwelski K, Rocken C, Roetzer I, Rohr P, Schepp W, Schlag PM, Schmid RM, Schmidberger H, Schmiegel WH, Schmoll HJ, Schuch G, Schuhmacher C, Schutte K, Schwenk W, Selgrad M, Sendler A, Seraphin J, Seufferlein T, Stahl M, Stein H, Stoll C, Stuschke M, Tannapfel A, Tholen R, Thuss-Patience P, Treml K, et al. German S3-guideline «diagnosis and treatment of esophagogastric cancer». Z Gastroenterol. 2011;49:461–531.

Park DH, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, Lee SK, Kim MH. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy. 2009;41:842–8.

Polkowski M, Larghi A, Weynand B, Boustiere C, Giovannini M, Pujol B, Dumonceau JM. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) technical guideline. Endoscopy. 2012;44:190.

Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. 2009;54:2330.

Romanelli DF, Beckmann CF, Heiss FW. Celiac plexus block: efficacy and safety of the anterior approach. Am J Roentgenol. 1993;160:497–500.

Runzi M, Niebel W, Goebell H, Gerken G, Layer P. Severe acute pancreatitis: nonsurgical treatment of infected necroses. Pancreas. 2005;30:195–9.

Seifert H, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. Lancet. 2000;356:653–5.

Seifert H, Biermer M, Schmitt W, Jurgensen C, Will U, Gerlach R, Kreitmair C, Meining A, Wehrmann T, Rosch T. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD study). Gut. 2009;58:1260–6.

Sharples L, Jackson C, Wheaton E, Griffith G, Annema J, Dooms C, Tournoy K, Deschepper E, Hughes V, Magee L, Buxton M, Rintoul R. Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. Health Technol Assess. 2012;16:1–82.

Sobin LH, Gospodarowicz MK, Wittekind C. UICC: TNM classification of malignant tumors. 7th ed. Chichester/West Sussex/Hoboken: Wiley-Blackwell; 2009.

Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). Gastrointest Endosc. 2008;68:1102–11.

Wang KX, Ben QW, Jin ZD, Du YQ, Zou DW, Liao Z, Li ZS. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointest Endosc. 2011;73:283–90.

Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis (EUS-CPN) in patients with pain due to intra-abdominal malignancy (IAM). Gastrointest Endosc. 1996;44(6):656–62.

Wilcox CM. Tinkering with a tarnished technique: isn't it time to abandon celiac plexus blockade for the treatment of abdominal pain in chronic pancreatitis ? Clin Gastroenterol Hepatol. 2012;10(2):106–8. Epub 2011 Nov 9

Will U, Meyer F. Endoscopic ultrasonography (EUS)-guided transluminal cholangiodrainage (EUCD) — a novel option of interventional endoscopy in the interdiciplinary management of obstructive jaundice. Zentralbl Chir. 2012;137:20–31.

Will U, Fueldner F, Thieme AK, Goldmann B, Gerlach R, Wanzar I, Meyer F. Transgastric pancreatography and EUS-guided drainage of the pancreatic duct. J Hepato-Biliary-Pancreat Surg. 2007;14:377–82.

Wyse JM, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol. 2011;29(26):3541–6.

Yasuda I, Nakashima M, Iwai T, Isayama H, Itoi T, Hisai H, Inoue H, Kato H, Kanno A, Kubota K, Irisawa A, Igarashi H, Okabe Y, Kitano M, Kawakami H, Hayashi T, Mukai T, Sata N, Kida M, Shimosegawa T. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: the JENIPaN study. Endoscopy. 2013;45:627.