EFSUMB Guidelines on Interventional Ultrasound (INVUS), Part II
Diagnostic Ultrasound-Guided Interventional Procedures (Short Version)

EFSUMB Leitlinien interventioneller Ultraschall (INVUS), Teil II
Diagnostische Ultraschall-gestützte Interventionen (Kurzversion)

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- spleen

Abstract
This is the second part of the series on intervention ultrasound guidelines of the Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). It deals with the diagnostic interventional procedure. General points are discussed which are pertinent to all patients, followed by organ-specific imaging that will allow the correct pathway and planning for the interventional procedure. This will allow for the appropriate imaging workup for each individual interventional procedure (Long version/ short version; the long version is published online).

Zusammenfassung
Der zweite Teil der Serie von Leitlinien der European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) zur interventionellen Sonografie beschreibt die Vorbereitung, Indikationen, Durchführung und Nachsorge ultrasound-gestützter diagnostischer Interventionen am Abdomen. Nach Darstellung allgemeiner, für alle Patienten gültiger Voraussetzungen werden organbezogene Bildgebung, Planung und Ablauf der verschiedenen diagnostischen Interventionen dargestellt (Langversion/ Kurzversion; die Langversion ist online publiziert).

Introduction
This is the second of three guidelines (parts I – III) within the framework of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines on Interventional Ultrasound (INVUS) describing percutaneous ultrasound (US)-guided diagnostic and therapeutic abdominal interventions. Part II gives evidence-based recommendations for the safe and efficient performance of US-guided diagnostic interventions based on the available evidence at the time of manuscript preparation. It is preceded by guidelines on general principles and necessities of INVUS (part I) [1] and followed by US-guided therapeutic abdominal interventions (part III) [2]. Methods of guideline development are described in the introduction to the EFSUMB Guidelines on Interventional Ultrasound (INVUS) [3]. 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].

General Principles of Diagnosis for Ultrasound-Guided Interventional Procedures
Diagnostic interventional ultrasound (INVUS) procedures are efficient, minimally invasive techniques with the purpose of acquiring a diagnosis. Ultrasound (US) is the ideal imaging modality to guide interventional procedures with several advantages: the absence of radiation and lack of potentially nephrogenic contrast agents, US is inexpensive and real-time imaging ensures the visualization of needles, thus improving diagnostic accuracy with a reduction of complications [4 – 6]. Details are given in part I [1].

Essential Rules
- There must be a clearly defined indication for the diagnostic procedure and the risk should not outweigh the potential benefits.
- Accurate planning for INVUS procedures is essential to avoid complications. The operator should select the image guidance and interventional access pathway with the lowest risk.
- INVUS procedures require informed consent.
- Normal coagulation indices and platelet count are necessary to reduce bleeding risk [7].
is no consensus regarding the threshold values that preclude interventional procedures, but platelet count < 50 000/µL and Quick time < 50 % are commonly used indices [8]. In patients with < 50 000 platelets, prior to a high-risk procedure (e.g. liver or kidney biopsy, nephrostomy, complex radiofrequency ablation (RFA)), a transfusion of platelets is necessary [9]. For patients undergoing a moderate risk procedure (e.g. chemoembolization, venous interventions, chest, lung and intra-abdominal biopsy, drainage, direct RFA, spine procedures) or low bleeding risk procedures (e.g. thoracentesis, paracentesis, superficial abscess drainage, venography), a platelet transfusion is recommended [7]. The International Normalized Ratio (INR) value should be corrected to < 2.0 prior to low-risk procedures and < 1.5 prior to moderate to high-risk procedures. In patients with a Quick time < 50 %, vitamin K or administration of fresh plasma is recommended before the procedure. In most abdominal INVUS procedures, it is recommended to discontinue antipatelet therapy in the peri-procedural period.

- **INVUS procedures** that have an increased risk of septic complications (e.g. prostate biopsy) should include prophylactic antimicrobials to reduce post-invasive procedure infection.
- The use of sedation has to be considered in non-cooperative patients or when performing an INVUS procedure where an immobilized patient is crucial. All personnel performing any interventional procedure must observe aseptic conditions, and the puncture site must also be sterile.
- Whenever possible, the use of continuous US guidance is recommended to reduce the risk of complications. The use of contrast-enhanced US (CEUS) or fusion techniques may be helpful in large tumors with necrosis, or in tumors that are invisible or poorly visible on grayscale US to improve the accuracy in obtaining adequate tissue samples [10 - 12].
- **Diagnostic interventional procedures** can often safely transgress the stomach and small or large bowel with fine needles (22 gauge) [13].
- Correct identification and suitable transportation of the tissue samples in an appropriate medium are essential.
- The most common complication of the INVUS procedure is puncture site pain requiring simple analgesia. A major complication is hemorrhage [14] and normal coagulation indices do not preclude bleeding complications.
- Following a diagnostic INVUS procedure, the patient should remain under medical observation to detect early complications.

**Multidisciplinary decision**

The multidisciplinary setting should be the standard to discuss INVUS procedures to confirm the necessity of the procedure, possible alternatives and complications.

**What defines the probability of performing an INVUS procedure?**

- Availability of a safe needle path governs the performance of an INVUS procedure.
- The target structure should be visible during the procedure.
- Risk of bleeding should be taken into account.
- Patient cooperation is needed.

**Fine needle biopsy or aspiration**

Different sample types may be obtained either with a fine needle biopsy (FNB) or FNA depending on indication and local protocol; cytology is often adequate but insufficient when tissue architecture is essential, e.g. lymphoma.

**Specimen preparation**

The preparation and care of specimens depend on the local laboratory services, proximity to the procedure room, and availability of specialist technicians.

**Cytology specimen preparation**

Perform 1 - 2 passes. For each needle pass performed, prepare ≥ 2 good quality slides, with fixation according to the standard of the local cytology laboratory.

**Histology specimen preparation**

Specimens should be submitted in an adequate amount of 10 % neutral-buffered formalin fixative. The volume ratio of fixative to specimen size is very important for proper preservation of the tissue, i.e., a minimum of at least twice the volume of fixative as tissue is required.

**Microbiology specimens**

A strict aseptic collection technique is necessary to avoid contamination. It is essential to obtain sufficient material for cultures [15] and perform the appropriate culture depending on the clinical suspicion.

**Follow-up imaging**

Immediate post-procedural imaging is not routinely recommended. Patients should be observed following a standard protocol in a dedicated unit with appropriately trained staff. Standard procedure-specific post-biopsy observation sheets which highlight the management of suspected complications should be available [16].

**Recommendation 1**

Informed consent is mandatory in all ultrasound-guided interventional procedures with variation of forms as indicated in general ethical and national legislative documents (LoE 5, GoR D). Strong consensus (100 %).

**Recommendation 2**

Specific assessment of bleeding risk and considerations for the use of blood products or other hemostatic agents must be individualized to the patient. The INR value should be corrected to < 2.0 prior to low-risk procedures and < 1.5 in moderate to high-risk procedures. In patients with < 50 000 platelets, a transfusion of platelets is necessary prior to high bleeding risk procedures (LoE 2a, GoR C). Strong consensus (100 %).

**Recommendation 3**

Repeat biopsy is recommended when there is an inconclusive result or insufficient or non-diagnostic material. Critical evaluation of the first attempt is mandatory before considering an optimized repeated procedure (LoE 5, GoR D). Broad agreement (94 %).
Recommendation 4
Adequate material for a microbiology specimen is essential, and should be collected in sterile tubes, with correct labelling to assure appropriate analysis (LoE 5, GoR D). Strong consensus (100%).

Recommendation 5
Post-procedural care is essential to detect complications and should be part of appropriate patient management (LoE 2b, GoR B). Strong consensus (100%).

Liver
Diffuse liver disease
Liver biopsy (LB) for diffuse liver disease can be performed percutaneously, laparoscopically or by a transjugular approach.

Percutaneous liver biopsy
Indications for percutaneous liver biopsy
1. Evaluation of chronic liver diseases for staging and grading
2. Confirmation of diagnosis and prognosis
3. Evaluation of abnormal liver function tests
4. Diagnosis of cholestatic liver disease
5. Evaluation of infiltrative or granulomatous disease
6. Post-liver transplantation to evaluate and manage rejection
7. Evaluation of unexplained jaundice or suspected drug reactions

Contraindications for percutaneous liver biopsy
1. Patient refusal or uncooperative patient
2. Ascites
3. Infection of the hepatic bed
4. Severe coagulopathy
5. Platelet count < 70 000/µL, transfusion is recommended [17].

Antithrombotic agents
Antithrombotic agents should be stopped or substituted before INVUS procedures, ensuring optimal risk/benefit ratio for the patient.

Post Liver Biopsy
After LB, a period of four hours of observation, including measurement of pulse and blood pressure, is recommended [17]. Performing LB in an outpatient setting is standard practice.

Technical aspects of a liver biopsy
Important aspects of percutaneous LB include:
1. LB under US guidance is safer than a blind biopsy [18–21];
2. LB specimen size is related to the diameter of the needle; a 15–18-gauge needle will provide sufficient portal tracts for histological diagnosis [22];
3. Operator experience has an influence on the quality of the sample [22, 23];
4. An optimal specimen should be ≥ 25 mm long and include ≥ 11 portal tracts [18].

Complications
Complications following LB performed by experienced operators are low [24]. The main complications following percutaneous LB are: pain, vasovagal reactions, liver hematoma (symptomatic or asymptomatic), hemoperitoneum, pneumothorax, hemobilia, bile leakage, organ perforation (gallbladder, colon) and arteriovenous fistula.

Laparoscopic liver biopsy
This can be performed during a laparoscopic procedure (e.g. cholecystectomy) or during a diagnostic laparoscopy. Diagnostic laparoscopy has the advantage that it visualizes the superior and inferior surfaces of the liver and enables guidance of the biopsy.

Transjugular liver biopsy
This is performed in patients at high risk of bleeding and in whom percutaneous LB is hazardous. The technique is complex and an experienced operator is needed. The quality of the specimen is essential for diagnosis. The rate of complications after this procedure is 1–20 %, with a mortality of 0.1–0.5 % [25].

Focal liver lesions
Despite the evolution of imaging methods, such as CEUS, contrast-enhanced computed tomography (CE-CT), contrast-enhanced magnetic resonance imaging (CE-MRI), as well as the availability of tissue elastography for focal liver lesion (FLL) assessment, histological evaluation is often required. FLL biopsy is performed under guidance (usually by US).

Indications for FLL biopsy
▶ Diagnosis not established on any imaging
▶ Lesion immune-histochemical analysis needed for therapy
▶ Histological assessment is needed for a therapeutic decision (e.g. hepatocellular carcinoma vs. cholangiocarcinoma).

Contraindications for FLL biopsy
Identical as for percutaneous LB.

Technique
The lesion is biopsied under US guidance, always passing through healthy liver, to avoid bleeding. The needle size used to biopsy an FLL can vary from thin needles 23–20 gauge for FNA to large needles 18–15 gauge for core biopsy.

Complications of FLL biopsy
Complications include shoulder pain, bleeding, tumor seeding, organ perforation (gallbladder, colon) and sepsis. The incidence of complications varies depending on operator experience, needle type and tumor location. More frequent complications include: pain (< 20 %) and liver hematoma (1–20 %). The following other complications are seldom encountered: intraperitoneal bleeding (< 1 %), pneumothorax (< 1 %), death (0.0083–0.03 %) [26, 27]. The risk of malignant seeding during biopsy is rare (0.003–0.009 %) [28, 29].

Recommendation 6
Liver biopsy is associated with a low rate of complications (LoE 2b, GoR B). Broad agreement (94%).

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Spleen

Introduction
Focal lesions of the spleen are rarely encountered but can be difficult to characterize. The risks of splenic biopsy are lower than generally thought and can be undertaken safely in most patients while achieving high levels of diagnostic accuracy. Percutaneous splenic biopsy carries significantly less risk than diagnostic splenectomy [30, 31].

Background
Focal lesions of the spleen are uncommon, encountered in only 0.2 – 1.0 % of abdominal US examinations [32].

Sonographic features
Focal lesions may be solid, cystic or mixed in nature. Although certain focal lesions have distinctive US features, definitive characterization is often impossible based on the clinical history, laboratory tests and imaging characteristics.

Contrast-enhanced ultrasound
The use of CEUS can be very helpful in identifying and characterizing focal splenic lesions, as summarized in previous guidelines [33].

Indications
The most common indications for biopsy are:
- Focal lesion in a patient with known or suspected lymphoma
- Focal lesion in a patient with known extrasplenic malignancy
- Focal lesions in immunocompromised patients
- Pyrexia of unknown origin with splenic abnormality
- Cystic lesion where there is concern of malignancy or abscess

Contraindications
Contraindications to biopsy include:
- Uncorrectable coagulopathy
- Lack of a safe biopsy pathway
- Uncooperative patient
- Hemodynamic instability
- Severe cardiopulmonary compromise

Materials and Technical Issues
Pre-biopsy planning
Prior to biopsy all imaging studies should be reviewed to identify the safest route of access. In patients with imaging abnormalities at multiple sites, a non-splenic biopsy site is usually preferred. A minimum platelet count of 50,000 – 70,000/µL, INR < 1.2 – 1.6 and APTT 20 – 33 sec are required [34, 35].

Biopsy technique
Biopsy is usually possible with local anesthesia. Subcostal puncture minimizes the risk of pleural transgression but higher punctures may be necessary to target specific lesions. Hemorrhage is minimized by targeting a peripheral lesion [35 – 37]. Lesions close to the splenic hilum are a relative contra-indication to biopsy.

Fine needle aspiration cytology versus core needle biopsy
Both fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) can be used [36, 38 – 43]. A meta-analysis involving 741 splenic biopsies in 639 patients [34] found that 95 % provided sufficient material for analysis, with an overall sensitivity of 87.0 % and specificity of 96.4 %. The results of FNB and CNB were similar except for lymphoma where CNB gave statistically superior results [44]. CNB needle size should be 18 gauge or smaller to minimize the risk of hemorrhagic complications [34, 45, 46]. The complication rate of 18-gauge biopsies does not appear to be greater than with smaller needle sizes and provides greater diagnostic accuracy [47].

Sample preparation
CNB samples are usually sent to the laboratory in formalin solution. Several FNAC aspirates are optimal for cytology prepared as 4 smeared air-dried slides and an aspirate in cytology collection fluid to allow preparation of a micro-pellet.

Post-procedure care
Post-procedure the patient should be carefully observed for a minimum of 4 hours. Discharge is possible at this stage [35, 37] provided that the patient is asymptomatic and discharged to a responsible caregiver.

Complications
The most common major complications are hemorrhage and splenic rupture. Rarely splenic biopsy may result in a pneumothorax. A meta-analysis of 859 biopsies in 741 patients calculated an overall complication rate of 4.2 % and a major complication rate of 2.2 % [34]. No reports of needle tract tumor seeding from splenic tumors were identified.

Recommendation 7
The discontinuation of acetyl salicylic acid (aspirin) is not necessary when performing a liver biopsy (LoE 2b, GoR B). Broad agreement (81 %).

Recommendation 8
Liver parenchymal biopsy should be performed with ultrasound, either guided or assisted (LoE 2b, GoR C). Broad agreement (88 %).

Recommendation 9
Focal lesions of the spleen are uncommon; definitive diagnosis based on imaging appearances may not always be possible and biopsy may be considered if a definitive diagnosis is required (LoE 3b, GoR C). Strong consensus (100 %).

Recommendation 10
Ultrasound is the imaging modality of choice for most splenic biopsy procedures (LoE 5, GoR D). Strong consensus (100 %).

Recommendation 11
Biopsy of focal splenic lesions has high levels of diagnostic accuracy. Overall, core needle biopsy is slightly superior to fine needle aspiration for cytology particularly if lymphoma is suspected (LoE 2a, GoR B). Strong consensus (97 %).
Recommendation 12

The complications of splenic biopsy are predominantly due to bleeding, with the complication rate of core needle biopsy being slightly greater than fine needle aspiration for cytology but lower than splenectomy (LoE 2a, GoR B). Strong consensus (100%).

Recommendation 13

For core needle biopsy a needle size of 18G or smaller should be used to minimize the risk of splenic bleeding (LoE 2a, GoR B). Strong consensus (100%).

Pancreas

Biopsy of focal pancreatic lesions

Solid pancreatic lesion

Patients with a ductal adenocarcinoma characterized as resectable on imaging should have no preoperative sampling performed (avoiding false-negative results) with surgical referral instituted [48 – 52]. Histopathological confirmation is necessary for inoperable pancreatic cancer and for patients who are unsuitable for surgery prior to non-surgical neoadjuvant treatments [53]. FNA or CNB can be performed to determine the Ki-67 value of neuroendocrine neoplasms for prognosis.

Cystic pancreatic lesion

Percutaneous sampling of cystic pancreatic lesions has limited evidence and endoscopic ultrasound (EUS)-guided sampling is performed in these cases [54]. EUS-FNA cytology is more accurate than fluid analysis in the differentiation of benign and malignant cystic pancreatic lesions. The combination of cytology and fluid analysis is the best method for malignant lesions [54, 55]. Cystic neoplasms requiring surgery with typical imaging appearances do not require EUS-FNA before resection; most pancreatic cystic tumors should be resected without the need for cystic fluid analysis [56].

Imaging and sampling accuracy

Focal pancreatic lesions (FPL) are initially identified on transabdominal US examinations. The addition of elastography may evaluate the stiffness of the lesion. A distinction between solid and cystic masses is crucial [57, 58]. Further evaluation of solid pancreatic lesions relies on CECT [59]. Better results for the diagnosis of ductal adenocarcinoma can be obtained when CT is combined with CEUS [60]. A percutaneous US-guided approach is preferred for minimal invasiveness, low cost, and duration of the procedure, and allows appropriate cytology assessment of solid lesions [61 – 63]. FNA is superior to core-needle or open biopsy. Cystic lesions that require pathological diagnosis are sampled via EUS [64 – 68]. The accuracy of percutaneous US–FNA of pancreatic masses reaches 99.4 % [61, 62, 69 – 73]. A sensitivity of 89 %, a specificity of 98 %, a positive predictive value of 99 %, and a negative predictive value of 74 %, for an overall diagnostic accuracy of 91 %, have been reported [63]. The accuracy of percutaneous sampling varies depending on the lesion position: 93 – 94 % for body-tail lesions, 83 – 84 % for head lesions [72, 74].

Indications

- Characterization of a solid unresectable pancreatic mass.
- Differential diagnosis between neoplasm and focal inflammatory conditions.
- Suspicion of an uncommon entity (i.e., metastases, lymphoma), even if resectable, which could be treated non-operatively.
- Ki-67 “quantification” for the prognosis of neuroendocrine neoplasms [75].
- Cystic lesions that are undefined or suspicious for malignancy after MR imaging evaluation, even if an endoscopic approach is preferable to address this issue.

Contraindications

- Coagulation disorders are absolute contraindications to pancreatic diagnostic interventional procedures.
- Patient refusal of any therapy is a contraindication for biopsy.

Ultrasound biopsy procedure

US evaluation of a lesion includes B-mode and Doppler imaging to evaluate content and identify the safe and most productive biopsy route, with CEUS aiding positioning in viable vascularized areas.

Complications

Percutaneous US-guided FNA complications are rare [62]. No major complications were reported in a multicenter study [63]. US guidance has lower complication rates as compared to CT guidance: 1.7 – 5.0 % versus 2.4 – 19.0 % [72 – 74, 76, 77]. The risk of tumor seeding is reported in both percutaneous and endoscopic procedures [78, 79].

Follow-up imaging

At the end of a percutaneous intervention, a complete US evaluation of the abdomen should be performed.

Pancreas parenchyma biopsy

Indications and contraindications

Diagnostic intervention is not required for the diagnosis of diffuse pancreatic diseases (i.e., acute and chronic pancreatitis) except for the diffuse form of autoimmune pancreatitis (AIP).

Diagnostic puncture for pancreatitis-associated fluid

Fine needle aspiration culture of pancreatic fluid collections is useful if the diagnosis is uncertain allowing optimized antibacterial therapy, but is not routinely indicated, as sampling has a 25 % false-negative result and rarely leads to an alteration in clinical management [80, 81].

Recommendation 14

In patients with a resectable pancreatic mass with typical imaging aspect of ductal adenocarcinoma, a preoperative sample should not be performed and patients should be directly referred for surgical evaluation (LoE 2b, GoR B). Strong consensus (100%).

Recommendation 15

Resectable pancreatic masses with atypical features at imaging should be referred for EUS and EUS-guided sampling (LoE 3b, GoR A). Strong consensus (97%).
Kidney

Introduction
Renal biopsy will be performed in both the native and transplant kidney [82].

Imaging modalities
Alternative imaging options should be considered as appropriate if US does not provide the required information. For drainage of an abscess or the collecting system and biopsy of the renal parenchyma in the assessment of renal impairment, US is adequate.

Multidisciplinary decision
The decision for INVUS related to tumor treatment should be made in an interdisciplinary tumor meeting.

What defines the possibility of performing an INVUS procedure?
The INVUS procedures for diagnostic workup are limited by absolute and relative contraindications. INVUS is available at a reasonable cost and in low resource settings, yet requires investigators experienced in the procedure [4].

Diffuse renal disease
Percutaneous renal biopsy has become the gold standard for the diagnosis and classification of diffuse renal diseases, in the absence of a major contraindication, particularly when specific treatment can be initiated [83].

Indications and contraindications
Indications
There is no generally accepted standard protocol for selecting patients for renal biopsy. The decision for renal biopsy is largely made by weighing therapeutic benefit against potential complications.

Contraindications
The most common contraindications for percutaneous renal biopsy are mentioned elsewhere [83].

Pathology
The biopsy report for non-neoplastic kidney diseases represents a complex integration of clinical data with light microscopy, immunofluorescence, and other (electron) microscopic findings. A renal biopsy specimen should always be interpreted within the context of the clinical presentation and laboratory findings.

Ultrasound guidance
Real-time US is superior to the “blind” approach (using US for localization only) with a higher diagnostic yield (100% vs. 84%) and a lower complication rate [5].

Biopsy technique
The choice of biopsy needle is largely one of individual preference. Most studies have been performed with semi-automated biopsy needles with a size of 14–18 gauge in order to ensure a sufficient number of glomeruli [84–88].

How many passes?
It is recommended to obtain two core renal biopsies from the lower pole of the left kidney in the absence of local contraindications, such as polar atrophy, arteriovenous fistula or cyst.

Needle size
Renal biopsy produces the highest diagnostic yield with more glomeruli per core biopsy using 14-gauge Tru-cut needles compared to 16- and 18-gauge needles without a difference in complication rates [84–88].

Fine needle aspiration cytology versus core needle biopsy
There is no role for FNAC in the evaluation of diffuse renal disease.

Post-procedural care
After biopsy, an observation time of 6 hours is thought sufficient but up to 24 hours may be considered in patients with a higher risk of bleeding.
Out- or inpatient
There is a trend to perform biopsies in outpatient clinics [89]. Post-procedural care is recommended for at least 8 – 12 hours, since 80 – 85 % complications occur within 8 hours [90 – 93].

Complications
High blood pressure, female gender, younger age, abnormal coagulation (prolonged bleeding time) and both acute and chronic renal failure are associated with a higher complication rate [94, 95].

Focal renal lesions
The differentiation between benign and malignant renal lesions is of utmost importance. Diagnostic biopsy success is reported between 75 – 100 % and has improved with a significant reduction of indeterminate biopsies (around 10 %) [96 – 98].

Indications
Renal lesion biopsy is indicated when management will change under the following circumstances:

▶ Small renal masses that are indeterminate on imaging
▶ Known extrarenal malignancy
▶ Candidates for active surveillance or local ablative techniques
▶ Metastatic disease to select the optimal systemic therapy when the renal tumor is the most suitable site
▶ Unresectable retroperitoneal tumors involving the kidney
▶ In infection without response to antibiotic treatment
▶ When partial vs. radical nephrectomy is discussed (solitary kidney)

Needle size
Usually 14- to 18-gauge core biopsy needles are used but data regarding complications following multiple biopsies are not available [99, 100]. The risk of track seeding has not been evaluated.

Contrast-enhanced ultrasound
The role of CEUS has been described in the EFSUMB guidelines and is useful to delineate necrotic areas [33].

Recommendation 23
Percutaneous renal biopsy should be performed under ultrasound guidance (LoE 3a, GoR B). Strong consensus (100 %).

Recommendation 24
Spring-loaded needles for native parenchymal kidney biopsies are superior to manual needles (LoE 2b, GoR B). Strong consensus (100 %).

Recommendation 25
Two adequate samples should be obtained with parenchymal kidney biopsies (LoE 3b, GoR B). Strong consensus (100 %).

Recommendation 26
18G needles should be used as they combine a high diagnostic yield and a relatively low complication rate in native kidneys (LoE 2a, GoR B). Broad agreement (90 %).

Adrenal Gland

Imaging modalities
Adrenal masses can be detected by transabdominal grayscale US with high accuracy [101 – 105]: 99 % and 69 % for the right and left adrenal glands, respectively [101]. Ultrasound, although sensitive, is not capable of accurately differentiating adrenal lesions [106]. Contrast-enhanced ultrasound for the characterization of adrenal masses has been evaluated [107, 108], demonstrating no specific patterns distinguishing benign from malignant lesions [107].

Multidisciplinary decision
Most adrenal masses not typical for adenoma and not characteristic for a pheochromocytoma on CECT and MRI may require biopsy, especially with a background of known or suspected malignancy [109, 110]. A biopsy of a possible pheochromocytoma is contentious because of the risk of severe hypertension [111] and clinical and laboratory evaluation is advised prior to biopsy [112 – 114].

Indications for adrenal biopsy

▶ Staging a known malignancy.
▶ Identifying an unknown primary malignancy.
▶ Differentiating benign from malignant lesions in equivocal cases [114].

Relative contraindications to adrenal biopsy

▶ Uncorrectable coagulopathy.
▶ Inability to reach the tumor using a safe path.
▶ An unsafe target [114, 115].

INVUS procedure
The benefits of US guidance include real-time multi-planar imaging, absence of radiation, low cost, portability, and the ability to rapidly confirm complications such as bleeding. The drawbacks of US guidance include inadequate visualization of the target or needle due to operator experience, lesion depth, or intervening bowel gas or bony structures. Use of US identifies the pleural reflection and lung edge to avoid diaphragmatic penetration [114].
Materials and technical issues
Routine pre-procedural blood investigations including full blood count (FBC), metabolic panel and coagulation studies (PT, PTT, INR) are performed.

Description of the intervention
Right-sided adrenal biopsies can be performed through a trans-hepatic, direct posterior or right-decubitus (target side down) approach. Left-sided adrenal biopsies can be approached with the patient in the left-decubitus position, posteriorly or anteriorily/ transgastric [116, 117]. Smaller FNA needles (21–23G) may be preferred when sampling hypervascular lesions, especially when surrounded by bowel or blood vessels, or in the setting of malignancy [118, 119]. If FNA is chosen, a capillary pass technique is used. Syringe aspiration may traumatize the lesion so that a bloody sample is obtained.

Role of cytology
The overall sensitivity of FNA in detecting the presence of malignancy is 85 % [120–122].

Complications
The most frequent complications following adrenal biopsy are hemorrhage and pneumothorax. The overall complication rate is 5.3 %. Most are minor, self-limiting complications. The rate of major complications requiring further treatment is 0.4–2 % [116, 117, 123].

Recommendation 30
Adrenal masses incidentally detected at US or indeterminate at CT should be characterized with MR imaging and/or PET imaging (LoE 2b, GoR B). Strong consensus (97 %)

Recommendation 31
An ultrasound-guided adrenal biopsy should be considered in lesions that are indeterminate at imaging (LoE 2b, GoR B). Strong consensus (100 %).

Recommendation 32
Prior to adrenal biopsy, pheochromocytoma should be excluded by biochemical assessment in patients with a clinical suspicion (LoE 5, GoR D). Strong consensus (100 %).

Gastrointestinal tract

Indications and contraindications
Most neoplastic lesions of the gastrointestinal (GI) tract develop as mucosal masses and endoscopic biopsy is the traditional procedure to characterize and obtain a tissue sample. Ultrasound or CT guidance is reserved for specific situations where an appropriate approach by endoscopy or EUS is not feasible [124]. The indications for US-guided biopsy of GI tract lesions are:
▸ Beyond easy reach of the endoscope (small bowel lesions)
▸ Submucosal, suberosal and exophytic lesions, especially gastritic tumors, e.g. gastrointestinal stromal tumors (GIST) or lymphoma
▸ Failed biopsy attempts by endoscopic means [124–126]
It is usually safe to pass through stomach and small bowel segments with 18-gauge needles [127].

Imaging modalities
EUS-guided biopsy is the procedure of choice for submucosal, suberosal, or exophytic lesions [128]. CT guidance may be preferred for some lesions, especially those located deep in the pelvis or behind a gas-filled bowel.

Multidisciplinary decision
The indication for US-guided biopsy of a GI tract lesion should be determined by a multidisciplinary team:
▸ Availability of advanced endoscopic techniques (i.e., EUS and enteroscopy) [129, 130]
▸ Suspicion of malignancy and assessment of operability
▸ Probability that the result of the biopsy will alter management (i.e., starting systemic antibiotic therapy in a tuberculous lesion instead of surgery)

Materials and technical issues
Sampling may be performed by means of FNA or core biopsy [124–126].

Results
Sensitivity and accuracy between 80–99 % have been reported for GI tract biopsies with large needles in retrospective series [124–126, 131]. Fine needles perform less well with sensitivities of 45–50 % [126]. To increase the sensitivity, CEUS guidance may be used in larger lesions (especially gastric GIST tumors) to target non-necrotic, viable tissue [132].

Complications
Complications are rare (<1 %) for GI tract diagnostic interventions and include hemorrhage and infection related to perforation [131].

Recommendation 33
GI tumors not characterized by endoscopic biopsy can alternatively be biopsied by percutaneous or endoscopic US guidance (LoE 4, GoR C). Strong consensus (100 %).

Peritoneal cavity and mesentery

Indications and contraindications
The peritoneum, including the omentum and mesentery, is a common site for secondary disease extension from adjacent visceral organs and distant metastatic deposits, and is an unusual site of primary neoplastic disease. Non-neoplastic processes (e.g. granulomatous diseases, hematomas, infectious or inflammatory conditions) may also involve the peritoneum, mimicking neoplastic disorders.

Imaging modalities
Contrast-enhanced computed tomography is the modality of choice for diagnosis, supplemented by MRI and PET/CT techniques [133]. Percutaneous imaging-guided biopsy is safe with a sensitivity of 93 %, specificity of 86 %, and negative predictive value (NPV) of 50 %. In patients with a known primary malignancy,
the sensitivity of the biopsy procedure is 93\%, the specificity is 100\% and the NPV is 38\%. In patients without a known primary neoplasm, the sensitivity is 96\%, the specificity is 75\% and the NPV is 75\% [134 – 136].

**Multidisciplinary decision**

Peritoneal mass biopsy should be considered at an early stage in the investigation of any patient with no diagnosis. Biopsy is not required if the mass is part of progressive disease and histological diagnosis has previously been obtained. Biopsy is performed if there is uncertainty of recurrence or possible new disease. Peritoneal masses in patients with a history of cancer are nearly always malignant (86\%) [136]. Biopsy is still indicated; 10\% of patients with a known primary malignant neoplasm will have a second malignant tumor. Biopsy is also indicated in patients without a known primary cancer; benign-appearing peritoneal tissue is predictive of a benign lesion in 75\% of cases [136].

**What defines the possibility of performing an INVUS procedure?**

The criteria for performing biopsy are a thick peritoneum or presence of a mesenteric mass on diagnostic imaging. The multiplanar capability of US allows the operator to avoid vessels, the bowel and solid viscera. CT should be reserved for small lesions or disease that is inaccessible to US.

**Materials and Technical Issues**

Peritoneal masses are localized with US using graded compression to displace overlying tissue and bowel, employing either a low-frequency or high-frequency transducer. The needle path is assessed with color Doppler US to ensure blood vessels are avoided. Local anesthetic (1 – 2\% lidocaine hydrochloride) can be administered subcutaneously into the abdominal wall. Fine needle aspiration is typically performed using 20 – 25-gauge needles and provides samples for cytologic examination, whereas CNB is performed using 16 – 20-gauge needles and provides tissue for histologic assessment [137].

**Complications**

In those patients with large-volume ascites, biopsy should not be performed until the ascites is reduced. The anatomical features of the peritoneum will result in a superficial location of the lesions, adhering to the abdominal wall, thus avoiding underlying organs during biopsy. Minor complications related to percutaneous biopsy procedures are seen in 2.7\% patients, unrelated to needle size.

**Follow-up**

In patients with a known malignancy, obtaining benign-appearing peritoneal tissue has a low NPV, which means that with a negative biopsy result a repeat biopsy or surgery should be considered to exclude a malignant process [136].

**Recommendation 34**

Imaging-guided percutaneous biopsy of the peritoneum is a safe and effective means of providing a tissue diagnosis (LoE 2b, GoR B). Strong consensus (100\%).

**Recommendation 35**

Ultrasound can be used for peritoneal mass biopsy (LoE 3b, GoR B). Broad agreement (87\%).

**Lymph Nodes**

**Indications and contraindications**

Cross-sectional imaging examinations reveal abdominal (mesenteric/retroperitoneal) lymph nodes with increasing frequency entailing further diagnostic workup as many neoplastic, inflammatory and infectious diseases produce abdominal lymphadenopathy [138].

**Imaging modalities**

Chest X-ray and CECT imaging of the neck, chest and abdomen are mandatory to evaluate the stage of the disease. Pathological analysis of the disease process is of paramount importance and is the reference standard for diagnosis [139].

**Multidisciplinary decision**

With any primary carcinoma it is important to identify abdominal lymphadenopathy as this affects staging and management. Lymph node biopsy is adequate for the diagnosis of metastatic carcinoma. In the assessment for lymphoma, an entire lymph node is desirable.

**What defines the possibility of performing an INVUS?**

Ultrasound-guided biopsy of abdominal lymph nodes is considered feasible if the lymph nodes are visible and a safe route is available [140] but CT-guided biopsy is the preferred technique [141 – 144]. CT-guided CNB is adequate to establish a diagnosis in 82.5\% of patients with lymphoproliferative disorders and should be deployed first in the diagnosis of any lymphoma [142]. Ultrasound allows continuous real-time visualization of the needle tip throughout the procedure, minimizing injury to adjacent critical structures and contamination with blood or extraneous tissue [145].

**Materials and technical issues**

Fine needle aspiration with adjuvant flow cytometry for diagnosing and sub-typing malignant lymphomas has been reported [139] but CNB provides additional diagnostic and prognostic information that may not be easily derived from FNA [146]. With CNB, a diagnostic rate of 83 – 96\% is reported for lymphoma and should be the procedure of choice for histological sampling in the absence of peripheral lymphadenopathy [147 – 149]. Core needle biopsy is performed most often with large core needles (≤ 14 gauge), while smaller needles (≤ 25 gauge) are used more readily for FNA.

**Description of technique**

Grayscale imaging and color Doppler are used to localize the lymph node and to select the shortest route free of vascular structures. Applying pressure with the transducer displaces and minimizes intervening bowel loops and fatty tissue. Usually two needle passes are performed, avoiding any necrotic area of the target lymph node. CEUS can be used [132]. The operator should
evaluate the specimen visually both before and after placing the sample into a 10% formalin solution.

Complications
An abdominal lymph node biopsy is usually well tolerated with a low rate of complications [142]. Local hematoma and post-procedural pain are described in 1.8% of cases, while bleeding requiring surgery is seen in 1% [150].

Follow-up
Patients must be monitored for 4 hours after biopsy procedures to check vital signs and assess for complications.

Recommendation 37
Percutaneous ultrasound provides accurate and safe guidance for abdominal lymph node biopsy (LoE 3b, GoR B). Strong consensus (100%).

Recommendation 38
Percutaneous core needle lymph node biopsy should be used as the method of choice if lymphoma is suspected (LoE 3b, GoR B). Strong consensus (100%).

Recommendation 39
In suspicious lymph nodes either core needle biopsy or fine needle biopsy/aspiration may be considered in the presence of known malignancy (LoE 3b, GoR B). Strong consensus (100%).

Retroperitoneum

Indications and contraindications
Retroperitoneal tumors cause symptoms or become palpable only when they have reached a significant size. The most common malignant lesions are sarcomas and lymphomas, while neurogenic tumors, paragangliomas and fibromatosis are the most frequently encountered benign lesions [151].

Other guiding modalities
CT-guided biopsy of retroperitoneal masses is well-established with good outcome. Fine needle aspiration guided by EUS has a high diagnostic accuracy with lower complications particularly for small lesions [152, 153].

Multidisciplinary decision
The decision to perform a biopsy of a retroperitoneal mass should be made by a multidisciplinary team consisting of a surgeon, oncologist and radiologist. Essentials to support this decision are: imaging features, potential resectability, the probability that the lesion is chemotherapy-sensitive (lymphoma, GIST) or a benign tumor and tumor size [151].

Materials and technical considerations
With US guidance an anterior approach must be used [154]. Due the risk of injury to large vessels (with subsequent intraperitoneal bleeding) or the bowel, fine needles are usually chosen.

Complications
In retroperitoneal tumors percutaneous US-guided FNA has a sensitivity of 67 – 95.8% depending on the frequency of different diseases in the study population [145, 155, 156]. The accuracy of FNA in diagnosing lymphoma, sarcoma and benign tumors is low. FNA is not indicated when these tumors are suspected [154]. The overall diagnostic rate of US-guided core biopsy was 88.5%. Using CT guidance core biopsy yields a correct diagnosis in 92 – 96% of cases [154, 157]. Complications include bleeding (intraperitoneal, retroperitoneal or in abdominal wall), injury of the bowel wall and pain.

Conclusion
In the management of retroperitoneal tumors, percutaneous biopsy should be performed in certain circumstances. Ultrasound is a valid guidance alternative to CT when biopsy is indicated.

Recommendation 40
In the case of indeterminate retroperitoneal masses (e.g. sarcoma), the indication for biopsy versus primary resection should be individually assessed (LoE 4, GoR C). Strong consensus (100%).

Recommendation 41
Ultrasound is a valid retroperitoneal biopsy guidance alternative to CT (LoE 4, GoR C). Broad agreement (87%).

Recommendation 42
An ultrasound retroperitoneal core biopsy is more accurate than fine needle aspiration and should be performed whenever possible (LoE 3b, GoR C). Broad agreement (84%).

Recommendation 43
Fine needle aspiration retroperitoneally either percutaneous or by EUS may be an alternative in difficult cases (LoE 4, GoR C). Strong consensus (100%).

Liver, renal, pancreas and bowel transplant

Imaging modalities
Ultrasound is the first-line imaging modality in evaluating all abdominal organ transplants to detect postoperative complications and most interventional procedures will be performed guided by US [158 – 161]. CT is crucial for the detection of fluid collections [162, 163], abscesses and fistulae.

Multidisciplinary decision
Multidisciplinary teams are involved from the preoperative evaluation and discussion of potential candidates in donor transplant programs to the management of complications throughout hospitalization and follow-up. The multidisciplinary team should include transplant physicians, surgeons, hemato-oncologists, histopathologists, and radiologists with experience in treating transplant patients.
Indications and contraindications

Liver transplant

Indications

▶ Percutaneous LB is indicated to diagnose diffuse parenchymal abnormality to differentiate between allograft rejection, reperfusion injury, drug-induced toxicity, viral infection or recurrent disease.
▶ FNA is indicated in the presence of perihepatic collections with suspicion of infection or bile leakage.
▶ FNB or FNA is indicated with suspicion of neoplastic complications (e.g., hepatocellular carcinoma or post-transplant lymphoproliferative disease (PTLD).
▶ Protocol LB with normal liver function is accepted to reveal unexpected abnormalities such as progressive fibrosis [164].

Kidney transplant

Indications

▶ Renal transplant biopsy is indicated when renal dysfunction is attributable to parenchymal disease, to differentiate between acute rejection and acute tubular necrosis as well as between chronic rejection and immunosuppression toxicity.
▶ Worsening of renal function or absence of improvement after treatment [165 – 167].
▶ Prior to altering immunosuppression treatment.
▶ Protocol transplant biopsies at 3 – 12 months despite normal renal function to diagnose subclinical allograft dysfunction [165, 168, 169].
▶ FNA is indicated in the presence of peri-renal collections with suspicion of infection.
▶ FNB or FNA are indicated with suspicion of neoplastic complications (e.g., PTLD).

Pancreas transplant

Indications

▶ Suspected rejection: persistently or significantly elevated blood glucose level and/or significant reduction in insulin level.
▶ Follow-up of rejection.
▶ Clinical protocol in some institutions.
▶ Suspicion of PTLD.
▶ FNA to differentiate between the different types of fluid collections (e.g., abscess).

Combined kidney/pancreas transplant

The majority of pancreas transplants are simultaneous pancreas-kidney transplants.

Indications

▶ Suspected rejection.
▶ Follow-up of rejection.

Bowel transplant

Surveillance endoscopies for the first few months after intestinal transplantation are performed and endoscopically guided biopsy is required for rejection [170 – 172].

Indications

▶ To differentiate between acute rejection, chronic rejection, infections, and a variety of other inflammatory conditions.

Contraindications to all transplant interventions

▶ Uncorrectable coagulopathy.
▶ Lesions not detected by US (contraindicated to perform the procedure by US). Fusion imaging with CEUS may allow this to be performed.

Guided biopsy in focal and diffuse lesions

Biopsies are indicated to diagnose diffuse parenchymal disease and post-transplant focal or diffuse neoplasia including organ malignancy or PTLD.

Description of the intervention

A variety of needles with different lengths and caliber can be used for INVUS procedures in transplant patients.

Liver transplant biopsy

A biopsy of a liver transplant is performed in the same way as a biopsy of a native liver [173, 174]. The most common serious complication is post-biopsy bleeding, occurring in < 0.3% of patients.

Kidney transplant biopsy

The lower renal pole area is preferred. A cortical tangential needle approach to the kidney is preferred, and the needle should remain within the cortex when the biopsy is sampled. The direction of the deviation of the needle caused by the bevel should be towards the periphery of the kidney to reduce the risk of bleeding [175]. Following a renal transplant biopsy, the patient should remain in bed and be monitored for ≥ 4 hours. Immediately after biopsy, color Doppler US or CEUS can identify any significant bleeding along the puncture tract which may be treated by US-guided compression [176]. CEUS may be helpful in diagnosing persistent ongoing bleeding, which may be treated by embolization.

Biopsy of pancreatic transplant

The pancreatic transplant may be located behind the bowel and firm transducer pressure often allows bowel displacement to visualize the transplant. The complications are hemorrhage and fistula formation.

**Recommendation 44**

Ultrasound should be the first-line imaging modality to detect postoperative complications in organ transplants (LoE 5, GoR D). Strong consensus (100%).

**Recommendation 45**

A biopsy of a liver transplant should be performed using ultrasound (LoE 3b, GoR B). Strong consensus (100%).

**Recommendation 46**

Percutaneous ultrasound-guided biopsy of a renal transplant is a low-risk procedure (LoE 3b, GoR B). Broad agreement (100%).
**Recommendation 47**

Color Doppler should be used prior to transplant biopsy to reduce the risk of vascular complications (LoE 5, GoR D). Broad agreement (86%).

**Recommendation 48**

Percutaneous ultrasound-guided pancreatic transplant biopsies are to be performed in expert transplant centers (LoE 5, GoR D). Strong consensus (96%).

**Intervention in the elderly**

When considering an invasive US-guided procedure in an elderly person (defined as > 75 years), the benefit of making a precise diagnosis should generally have impact on the treatment plan. Based on the current limited literature focusing on the outcome of INVUS in elderly patients, ultrasound-guided tissue sampling and treatment is as safe and accurate as in younger patients (177 – 180).

**Recommendation 49**

The accuracy and complication rate of interventional ultrasound are similar in elderly (> 75y) and younger patients. US-guided therapeutic procedures may replace more invasive and radical treatment methods, with an adequate outcome and better patient tolerance (LoE 4, GoR C). Strong consensus (100%).

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