Percutaneous Gallbladder Biopsy: Indications, Technique and Complications

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Abstract: Gallbladder percutaneous tissue sampling is a not-so-common technique in cytohistological diagnosis of gallbladder tissue or masses, which can be useful in cases of surgically unresectable disease and unfeasible endoscopic assessment to address the most adequate chemotherapy course. Nonetheless, gallbladder percutaneous tissue sampling can be of great utility in the patient’s diagnostic and therapeutic work-up. This article summarizes the literature evidence on gallbladder biopsy techniques, complications, and technical precautions for a safe and effective sampling.

Keywords: interventional radiology; gallbladder; percutaneous biopsy; interventional oncology; tissue sampling; bile peritonitis

1. Introduction

Gallbladder cancer is a rare disease; nevertheless, it represents the most common and aggressive malignancy of the biliary tract, with the shortest median survival duration at the time of diagnosis of 6 months and a 5-year survival rate of 5% [1,2]. Complete surgical resection, the only potentially curative treatment, can be accomplished only in those patients who are diagnosed at an early stage of the disease. Therefore, early diagnosis is crucial to improve the survival rate, and investigation and assessment of every suspicious gallbladder polyp is necessary [3]. Most gallbladder cancers are incidentally diagnosed during endoscopic procedures or after surgical removal of the gallbladder for gallstones [4,5]. However, endoscopic or surgical approaches cannot always be feasible; in addition, due to the scarce and vague symptoms, some neoplasms are detected in a late/advanced stage, when they are no longer surgical candidates [6,7]. Moreover, the gallbladder can also be the site of secondary metastatic lesions from other neoplasms. When surgery or endoscopic diagnosis or intervention is not feasible, histopathological diagnosis is mandatory for the decision of the therapeutic approach, particularly to choose the correct chemotherapy drug. In these cases, a percutaneous approach can be crucial to obtain a correct diagnosis. In this article we summarize some of the most common gallbladder biopsy techniques, most frequent and feared complications, as well as the technical precautions to avoid them.

2. Materials and Methods

2.1. Indications

Current guidelines for gallbladder tumors offer differing recommendations on the diagnosis of gallbladder cancer. Surgical resection of gallbladder tumor is the gold standard for both histological diagnosis and treatment, avoiding the need for preoperative tissue sampling [8]. In case of unfeasible surgery or unresectable disease, tissue diagnosis
is recommended: diagnostic imaging plays a role in pre-operative diagnosis. However, distinguishing between benign or malignant lesions can be very challenging; in this case, tissue sampling can be of great help. The European Society of Medical Oncology (ESMO) guidelines recommend Endoscopic Retrograde Cholangio-Pancreatography (ERCP) biopsy for tissue diagnosis [9]. However, surgical resection and endoscopic biopsy are not always feasible: this occurs when endoscopic access is unsuccessful, impracticable with a trans-oral route, or in a difficult-to-approach gastrointestinal anatomy such as in case of previous surgery as Billroth-II or Roux-en-Y gastrojejunostomy; in case of biliary stones larger than 1.5 cm; or when surgical approach is not feasible (e.g., advanced/metastatic neoplasm). Compared to surgical resection, percutaneous image-guided biopsy of gallbladder lesions is a less invasive alternative to obtain diagnostic material [10]. Tissue sampling is mandatory in case of unresectable mass or in case of unfeasible endoscopic approach, to determine the nature of the neoplastic lesion, as well as to guide the choice of the most suitable chemotherapy drug, both in case of primary and secondary gallbladder malignancies. In addition, sometimes a pre-operative differential diagnosis between benign and malignant gallbladder lesions extended to the liver can be challenging, as in case of xanthogranulomatous cholecystitis; in these cases, if ERCP is unfeasible, percutaneous biopsy may be a valid tool to avoid aggressive surgical resection in case of benign findings [11].

The diagnosis of gallbladder cancer can be established by percutaneous fine needle aspiration (FNA) or core biopsy (CB), most frequently under ultrasound (US) guidance, and occasionally under computed tomography (CT) guidance [5].

The diagnostic yield of a percutaneous biopsy is relatively high, with a reported success rate greater than 90%, and low patient’s risks as minor abdominal pain (4.5%) and bile peritonitis (1 ± 6%) [6,7].

The experience of Van Sonnenberg and colleagues in performing diagnostic aspiration of gallbladder fluid, biopsy of gallbladder mass, and drainage of an infected gallbladder supports the feasibility and effectiveness of interventional radiologic techniques for benign and malignant gallbladder disorders, when surgery and endoscopic options are unfeasible [12].

2.2. Technique

The percutaneous needle biopsy (PNB) of gallbladder represents a diagnostic challenge and is not a routinely performed procedure; therefore, even an interventional radiologist with great experience in percutaneous biopsy of other organs could find it challenging [13,14].

The adopted imaging guidance greatly depends on physician’s preferences; however, gallbladder tissue characterization is usually performed under US guidance. Exceptions and obstacles to US guidance can be determined by an abnormal gallbladder position, or due to stomach or bowel interposition; in these cases, CT or cone-beam guidance in addition to US can be of great help to avoid bowel perforation or non-target structures.

The most frequently used type of needles in gallbladder tissue sampling are fine aspiration needle (usually from 25 to 20 gauge) and Tru-Cut core biopsy needle (usually from 20 to 14 G); coaxial and steerable needles can also be used [15]. As the needle can vary, so does the sampling technique; choice of the best technique is up to the operator, based on lesion size and location, as well as on patient’s bleeding risk and needle type:

- **Core biopsy (CB):** able to extract more appropriate tissue specimens for histologic analysis.
- **Fine-needle aspiration (FNA):** using a small needle (usually 23–22 G) with inner stylet, removed before withdrawing the sample; the specimen is usually of small quantity, and is used for cytology sample, smeared on glass slides [16–20].
- **Exfoliative cytology of bile aspirates:** easy to obtain, avoids direct puncture of the neoplastic lesion, and can provide a reliable diagnosis as most patients present with advanced-stage masses which have exfoliated in the adjacent bile [14].

Core biopsy, due to the greater gauge of the used needle, is bound to lead to greater complications than FNA; however, physician’s expertise on tissue sampling as well as the correct choice of the sampling technique can greatly reduce these drawbacks, as discussed below.
A combination of sampling techniques could lead to better outcomes, as demonstrated in biliary duct lesions. Ahmed et al. found that combined biopsy plus brush cytology is more effective in the diagnosis of malignant biliary strictures [5].

Use of coaxial technique, in which the biopsy needle (inner) is introduced into a guide needle (outer), can grant more than one sampling using the same route, increasing the amount of tissue specimens without increasing the puncture-related risks.

Technical and clinical success of PNB are defined respectively as the acquisition of sufficient material to establish a diagnosis and guide treatment decisions, and as the patients outcome depending on the results of biopsy in terms of appropriateness of medical or surgical management, according to specific guidelines [15].

Pericholecystic fluid collections or ascites can represent an obstacle to tissue sampling, as it increases the risk of bleeding or bile leak; care must be taken in finding a safe pathway to the gallbladder avoiding the pericholecystic fluid. In case of massive ascites, paracentesis or US-guided percutaneous drainage of the fluid can be performed before gallbladder biopsy.

2.2.1. Procedural Steps

The gallbladder is anatomically covered in its upper portion by liver parenchyma and, in the lower aspect, by peritoneum. Pre-procedural planning is crucial, both for choosing the best route (intercostal or subcostal, trans-peritoneal or trans-hepatic), as well as the most indicated sampling technique. As the gallbladder is a relatively non-fixed organ, susceptible to movements during needle puncture, automatic or semi-automatic needles should be preferred. Skin should be thoroughly sterilized before the procedure. Administration of local anesthetic superficially to the skin and subcutaneous tissues is advised, to avoid pain and to obtain a better compliance of the patient. PNB can then be performed, with the physician choosing the most suitable needle and technique, as well as the number of samples (depending on adequacy of specimens). In case of FNA, at least two needle passages should be performed (up to 4) [21]. In case of both FNA and CB, coaxial technique can be helpful to safely obtain more than one sample with a single gallbladder wall puncture, minimizing the risk of bile leakage; the outer needle can also act as an aspiration needle, allowing discrete bile sampling for cytological analysis. The risk of complications can be further minimized under US-guidance, giving real-time information on needle positioning, as care should be taken not to puncture the opposite/posterior wall of the gallbladder, which would increase the risk of bile spillage and peritonitis; care must be taken also in identifying and avoiding the adjacent cystic artery [18]. After sampling, the pathologic tissue is kept in a plastic container with fixative (usually 4% formaldehyde) and sent to pathology for histological examination.

2.2.2. Anticoagulant Management

According to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) consensus guidelines for the periprocedural management of thrombotic and bleeding risk, percutaneous biopsies, regardless of the organ, are considered high-bleeding risk procedures and need to be performed in a scheduled regimen [22]. This also applies to gallbladder tissue sampling: prothrombin time (PT) and international normalized ratio (INR) are routinely recommended to assess patient’s coagulation status. INR should always be below 1.5–1.8. Platelet count and hemoglobin are also routinely recommended, with a platelet threshold greater than 50 × 10^9/L. Threshold values are different in patients with chronic liver disease, in which adequate values of INR and platelet count are respectively below 2.5 and greater than 30 × 10^9/L. Among anticoagulants, unfractionated heparin should be suspended 4–6 h before procedure and reinitiated 6–8 h after; low molecular weight heparin (e.g., enoxaparin) should be limited to 1 in case of prophylactic use or 2 doses 24 h before procedure in case of therapeutic use. Anticoagulants should be reinitiated at least 12 h after the procedure. Warfarin should be withheld for 5 days, until a target value of INR lower than 1.8 is reached, and resumed the day after procedure. Bridging should be
considered in case of high thrombosis risk. Among antiplatelet agents, aspirin alone or in combination (e.g., aspirin/dipyridamole) should be withheld 3 to 5 days before procedure and resumed the day after procedure. Clopidogrel and Ticagrelor should be withheld 5 days before procedure, while Prasugrel should be withheld 7 days before. Anticoagulant and antiplatelet drugs’ half-life, suspension times, and side or rebound effects must always be specifically assessed.

2.3. Complications

Image-guided PNB is considered a minimally invasive and safe procedure, with a procedure-related mortality rate lower than 0.05% [15]. PNB complications are divided by the Society of Interventional Radiology (SIR) into minor and major, depending on their management and consequences [23]. Moreover, PNB complications can be divided into generic, which might occur with any percutaneous biopsy (such as skin discomfort, pain, vagal reaction, bleeding, and infection), and organ-specific complications that, in case of gallbladder PNB, are the results of the intervention on the biliary tract (such as bile leakage and bile peritonitis, as well as venous and arterial hemobilia).

2.3.1. Pain

Percutaneous gallbladder puncture can be associated with minor abdominal pain (4.5%) [6,7]. Pain usually considerably lessens after several days and eventually decreases over time, sometimes requiring analgesics, as shown by Tudyka et al. [24]. Moreover, pain may result from intercostal puncture and irritation of the periosteum and neurovascular bundle of the adjacent ribs. The irritation will usually resolve after a couple of days. If possible, a subcostal approach should be preferred if the anatomy is favorable [25].

2.3.2. Infection

Bacteremia is a known risk of biliary interventional procedures and can occur in up to 1.8% of patients [25]. The extreme consequence of bacteremia, sepsis, is one of the leading causes of death [26]. The interventional radiologist must be attentive to any patient showing clinical evidence of fever and chills; patients may become septic if not treated with appropriate antibiotics in the immediate post-procedure observation period [25]. Sterility is paramount to avoid infectious complications. Prophylactic antibiotics are not routinely administered for PNB, since the risk of contamination is low when the procedure is performed under sterile conditions. However, antibiotic prophylaxis can be indicated in immunocompromised patients [15]. Conversely, some authors suggest antibiotic prophylaxis before any procedure, deeming it essential to reduce the risk of bloodstream infective seeding [25].

2.3.3. Bile Peritonitis

Bile peritonitis is one of the most described complications of percutaneous procedures involving the gallbladder and can become very serious if not detected early [18,27,28]. The planning of gallbladder PNB should avoid, if possible, the trans-peritoneum route, due to increased peritonitis risk, whereas the trans-hepatic route should be preferred, also granting better stability; however, various authors have demonstrated that in the hands of experienced physicians the trans-peritoneum approach has very low risks [14,16,18]. The risk of bile peritonitis can be further minimized by not puncturing the opposite/posterior wall of the gallbladder, which would increase the risk of bile spillage and peritonitis [18].

2.3.4. Hemorrhage

Significant bleeding is a rare complication of PNB but is considered, along with sepsis, one of the two leading causes of death [26]. Using a trans-hepatic route to gain access to the gallbladder lumen, almost inevitably small hepatic and portal vessels are crossed. The risk of bleeding can be minimized under US-guidance, which gives real-time information on needle positioning, also allowing the identification of small hepatic and portal vessels, as well as the cystic artery [18]. Moreover, to reduce the hemorrhagic risk,
evaluation of the patient’s coagulation status is mandatory. When possible, antiplatelet or anticoagulant medications should be discontinued before the procedure; when cessation of these medications is problematic or unfeasible, risks and benefits should be carefully evaluated, and patients should be informed of the potentially increased risk of bleeding [15].

2.3.5. Tumor Seeding

In order to determine malignant cell seeding, viable neoplastic cells must be freed from the primary lesion, carried outside the gallbladder, and grown in a viable environment. Although malignant cell peritoneal dispersion has not been documented before in gallbladder biopsies or FNAB, the risk of tumor seeding can be the same as other percutaneous biopsies, as in pancreatic cancers, leading to disease diffusion and poor patient prognosis. According to the literature, risk factors for malignant cell seeding along the trocar route in case of laparoscopic cholecystectomy were peri-hepatic ascites and gallbladder adenocarcinoma histology; therefore, these risk factors should be taken into account even during percutaneous biopsy [29]. Nevertheless, the best preventive measure for tumor seeding is performing the percutaneous tissue sampling only when strictly needed, thoroughly considering risks and benefits of the procedure before every percutaneous biopsy. Coaxial technique, using an outer cannula-needle which remains in the gallbladder lumen which allows multiple samplings while protecting the healthy tissue, should always be preferred in order to avoid or strongly reduce the risk of extra-visceral spreading of malignant cells [30].

3. Discussion

Endoscopic intraluminal brush or forceps biopsy can be of great help to characterize gallbladder tissue, particularly in case of flat lesions; however, endoscopy is not always feasible due to unfavorable anatomy or previous surgery [5]. At the same time, surgical (laparotomy or laparoscopy) approaches can be hindered by patient comorbidities and tumor stage.

In the setting of unfeasible surgery and unpracticable endoscopic approach, percutaneous gallbladder biopsy can be of great help in providing specimens for histopathological diagnosis, which are necessary in differentiating primary and secondary gallbladder malignancies, in the choice of the best chemotherapy drug. In a 1982 study, Phillips et al. already showed feasibility of gallbladder puncture for various purposes in five patients (ranging from bile duct evaluation in case of hypersensitivity to intravenous contrast medium, to microbiological and cytological evaluations, and to evaluation of gallbladder lumen for masses), complicated by a bile leak in two cases [19].

Heterogeneous sensitivity of sampling techniques, as reported in the literature (even though mostly on bile duct neoplasms), is associated with different and high rates of false negatives, without consensus on which is the gold standard [31–33]. Zargar et al. obtained a diagnostic rate of 88.5% for US-guided FNA of gallbladder masses with 22 or 23 G needles [10]. In a study by Pandey et al., a sensitivity of 90% and 89% was found for FNA and Tru-Cut core biopsy of gallbladder lesions, respectively [34]. Rana et al. performed ultrasound FNA for the diagnosis of suspicion malignancy in 596 patients, with 23–22 G needle, and only 46 were inadequate for diagnosis, underlining that ultrasound FNA is an accurate method for diagnosing gallbladder lesions (mass or wall thickening) [16]. In a study on 433 patients by Chandra et al., a total diagnostic rate of 86.9% was found for benign and malignant gallbladder masses, with a concordance of 94.4% for histopathological analysis in malignant cases [21]. Selhi et al. reported a diagnostic rate of about 94% (44/47 diagnostic specimens) after US-guided FNA of gallbladder masses [35]. In a systematic review on FNA of gallbladder lesions, Koimtzis et al. found a pooled sensitivity and specificity of 0.85 and 0.94 respectively, without differences between transabdominal or endoscopic US guidance [3].

The role of percutaneous gallbladder FNA or biopsy for the diagnosis of suspect masses or tissues is still controversial, as some authors argue that this approach increases the risk of bile peritonitis [28]. Bile peritonitis was already defined by Van Sonnenberg et al. in
1982 as a feared complication, although in their experience with 33 patients who underwent a variety of percutaneous procedures involving the gallbladder (biopsy, bile aspiration, and cholecystography) with 22 or 20 G needles it was not encountered [12]. Zargar et al. observed a low rate of bile peritonitis using a 22 or 23 G needle (1 in 88 patients) [10]. Moreover, various authors report complication rates of transabdominal US-guided FNA or biopsy similar to the endoscopic approach [3,34,36].

Liquid bile biopsy could represent a powerful tool for diagnosing gallbladder cancer in patients unsuitable for both endoscopic, surgical, and percutaneous histopathological assessment, with promising future perspectives [37].

In conclusion, even though gallbladder percutaneous needle biopsy has very limited indications, it has a good diagnostic potential and represents an important procedure which should be present in every interventional radiologist’s toolbox. Performing a successful percutaneous gallbladder biopsy requires full knowledge of biliary and hepatic anatomy, considerable skill in the use of different types of techniques, and interventional patient management skills. Severe morbidity and, rarely, death can occur, and the interventional radiologist needs to be aware of all potential complications to minimize their occurrence.

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