Biopsy of focal liver lesions : guidelines, comparison of techniques and cost-analysis

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Abstract

When a focal liver lesion is discovered, differentiation between a benign and malignant nature and further characterization are mandatory to guide further treatment. Histology remains the golden standard. Improving imaging techniques such as contrast enhanced Doppler ultrasonography, spiral CT and new MRI procedures are promising, but not 100% accurate. When there is any doubt, biopsy should be performed. Fine Needle Aspiration Biopsy (FNAB) has a high sensitivity and specificity (90-95%) in experienced hands, but has a high insufficient sampling rate (up to 15%). In a series of 245 Fine Needle Tru-cut Biopsies (FNTCB) of focal solid liver lesions performed at our institution, sensitivity and specificity for the diagnosis of malignancy were 86% and 100% respectively, with an overall accuracy of 88%. Positive predictive value was 100%, but negative predictive value was rather low (56%). Insufficient sampling rate was low (2.5%), and a more accurate histological characterization was possible compared to FNAB. Finally, the cost-analysis of different biopsy techniques is presented for the Belgian situation according to used materials, pathology procedures and hospitalization. (Acta gastroenterol. belg., **2003**, 66, **160-165**).

Key words : focal liver lesion, fine needle biopsy, cost-effectiveness.

Introduction

Focal liver lesions, whether diagnosed in a normal liver or detected in a patient with a chronic liver disease, must always be characterized in order to establish the necessity and modalities of an appropriate treatment. For most but not all lesions histology is the golden standard to determine their exact nature. Therefore biopsy of a focal lesion is often performed to differentiate between benign and malignant lesions, and to establish the correct histological diagnosis.

For some lesions, however, imaging techniques are as accurate as the biopsy to make a correct diagnosis, and sometimes biopsy does not add diagnostic value to imaging or combined clinical, laboratory and imaging criteria. On the other hand, biopsy of a focal lesion can be accompanied by haemorrhage, pneumothorax and other complications. Needle tract seeding, with a possible negative impact on the patient's prognosis, is a complication of major concern. Finally the differences between patients with and without underlying chronic liver disease may add to the diagnostic value of some tests, all influencing the need for a biopsy to confirm the diagnosis.

In this article, we would first like to review the indications, non-indications and contra-indications for performing a biopsy of a focal liver lesion, taken into account the considerations mentioned above. When the indication is established, the choice can be made between different techniques to procure material for cytological or histological examination. A fine needle technique, using by definition a needle with an outer diameter of ≤ 0.9 mm (≥ 19G), is preferred, because of the higher complication rate of larger needles. The 3 different fine needle techniques [Fine Needle Aspiration Biopsy (FNAB), Fine Needle Cutting Biopsy (FNCB) and Fine Needle Tru-cut Biopsy (FNTCB)] and their differences in accuracy, insufficient sampling rate and possibility of histological characterization will be discussed. The economical impact of medicine being of increasing importance, we will finally assess the aspects of costs of the different biopsy techniques.

1. Indications, contra-indications and non-indications of biopsy of a focal liver lesion

Multiple factors influence the need to perform a biopsy of a focal liver lesion. Guidelines will therefore have to take into account the contra-indications for performing a biopsy, the possible complications of the biopsy, the diagnostic value of imaging techniques, the diagnostic value of the percutaneous ultrasound or CT-guided biopsy itself and finally the implications of therapy or the absence of therapy.

1.1. *Contra-indications to percutaneous liver biopsy*

According to Bravo *et al.*, absolute and relative contra-indications to perform a percutaneous biopsy of liver tissue and of a focal liver lesion can be defined (1). They are summarized in table 1. A suspected haemangioma or other vascular tumour should not be punctured because of the increased risk of bleeding.

1.2. *Complications of percutaneous liver biopsy*

Complications of liver biopsy in general and of biopsy of focal liver lesions in particular are rare, and can be very diverse. The most important complication is haemorrhage and its related mortality. Smith reviewed

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Table 1. — **Contra-indications to percutaneous liver biopsy**

Absolute contra-indications :
Uncooperative patient
History of unexplained bleeding
Tendency to bleed
Prothrombin time ≥ 3-5 sec more than control
Platelet count < 50×10^9/L
Prolonged bleeding time (≥ 10 min)
Use of a nonsteroidal anti-inflammatory drug within previous 7-10 days
Blood for transfusion unavailable
Suspected haemangioma or other vascular tumour
Inability to identify an appropriate site for biopsy by percussion or ultrasonography
Suspected echinococcal cysts in the liver
Relative contra-indications :
Morbid obesity
Ascites
Haemophilia

4 published large series of fine needle biopsies of abdominal structures, with very low mortality rates (0.031% in 16,381 patients ; 0.006% in 63,108 patients ; 0.008% in 9,212 patients and 0.018% in 10.766 patients) (2). There were in total 33 deaths, 21 of which related to liver biopsy, and of those 17 due to bleeding. The overall mortality risk of 0.033% is considered to be low, making liver biopsy a safe procedure if contra-indications are respected.

Except for right upper quadrant pain other complications are rare and of a various nature : haemobilia, haemothorax, pneumothorax, subcutaneous emphysema, bile peritonitis, bile pleuritis, infection, subphrenic abscess, pancreatitis due to haemobilia, anaphylaxis in case of an echinococcal cyst, and breakage of the biopsy needle.

In case of a malignant focal liver lesion, needle tract seeding is a specific complication of particular interest.

1.3. *Needle tract seeding*

Needle tract seeding after percutaneous biopsy of a malignant focal liver lesion is an important complication, as it may turn a localized, potentially treatable disease into a by definition metastatic disease. It may thus have a dramatic impact on disease prognosis, making this an important factor in the decision to perform a biopsy.

In the 4 series reviewed by Smith the reported frequencies for needle tract seeding in fine needle biopsy of all kinds of abdominal lesions were 0.005%, 0,006%, 0.003% and 0.009% respectively, mostly in cases of pancreatic lesions (2).

Pelloni *et al.* (3) reported in a review of needle tract seeding in fine needle biopsy for the suspected diagnosis of hepatocellular carcinoma (HCC) frequencies from 0.6% up to 5.1%, the latest result reported by Takamori in a series of 91 patients with confirmed HCC (4). They occurred between 1 and 72 months after the biopsy. Occurrence was not related to tumour grading, diameter of the nodule or the number of punctions, but only to the thickness of the covering parenchyma. It was mostly the sole tumour recurrence, was curable and did therefore not influence prognosis.

In a series of 455 biopsies in 420 patients with the final diagnosis of HCC, Huang *et al.* reported 9 cases (2%) of spread to the abdominal or chest wall 1.5 to 3 years after biopsy, cured by local resection or radiotherapy (5). Durand *et al.* noted 2 cases of needle tract seeding in 122 patients (2%) who underwent resection or transplantation for HCC after biopsy (6). In both cases it were subcutaneous lesions that could be cured by local excision. There was no recurrence nor could any other metastasis be detected.

Needle tract seeding has also been reported in colonic liver metastasis (7) and carcinoid tumour (8). The reported frequencies are low. As those lesions are only diagnosed in patients that have a rather long follow-up and hence a better prognosis, the real frequency is probably underestimated. One can imagine that patients dying early of their underlying disease may have undiagnosed needle tract seeding, the presence of which, however, being of little impact in those circumstances.

We may conclude that, although needle tract seeding exists, it is rare and consists of a local curable recurrence not influencing prognosis. When a focal liver lesion is punctured to perform a percutaneous ethanol injection (PEI) or a radiofrequency ablation (RFA), the needle tract should also be treated to prevent seeding. Surveillance of the puncture site is mandatory. Therapy of a needle tract lesion may consist of excision, ethanol injection or radiofrequency ablation (3,5,6). It is possible that the type of needle used or the thickness of the overlying parenchyma may influence the risk of needle tract seeding, but further studies are warranted to clarify their role.

1.4. *The diagnostic value of imaging techniques*

Little published data exist about the accuracy of different imaging techniques in the diagnosis of focal liver lesions. Most of the articles focus on one technique and present small series of selected patients, in whom diagnosis was already made by other techniques, and therefore do not always indicate the real value of those techniques in an unselected patient.

Torzilli *et al.* analyzed the results of imaging techniques (ultrasound, spiral CT and if necessary angiography, lipiodol CT or MRI) in 160 patients with 225 focal liver lesions referred for surgery (9). In 98.2% (221/225) the initial diagnosis was confirmed by post-operative histological findings, and the indication for surgery was correct in 97.5% (156/160) of cases. The results for the diagnosis of HCC, metastasis and cholangiocarcinoma are summarized in table 2. Even in this series an important selection bias must be noted, however, as the patients were specifically referred for surgery and thus had undergone a preliminary selection.

Table 2. — **Results of the preoperative evaluation by imaging techniques (ultrasound, spiral CT, angiography, lipiodol CT or MRI) confronted with post-operative histological findings, by Torzilli *et al.* (9)**

	Accuracy	Sensitivity	Specificity	PPV	NPV
HCC	99.6	100	98.9	99.3	100
Metastasis	99.1	100	98.8	96.9	100
CC	99.6	100	99.5	91	100

(PPV : positive predictive value, NPV : negative predictive value, HCC : hepatocellular carcinoma, CC : cholangiocarcinoma).

Table 3. — **Results of the different biopsy techniques of focal solid liver lesions according to Michielsen *et al.* (11)**

Technique	N° articles	Sensitivity	Specificity	Accuracy	NPV	ISR
FNAB	10	78-93	71-100	76-95	48-84	0-7.5
FNCB	5	81-94	86-100	91.5-96	84-88	1.3-29.5
FNTCB	4	90-94	100	91-99	81-98	0-6,7

(FNAB : Fine Needle Aspiration Biopsy, FNCB : Fine Needle Cutting Biopsy, FNTCB : Fine Needle Tru-Cut Biopsy, NPV : negative predictive value, ISR : insufficient sampling rate).

Fracanzani *et al.* followed 500 cirrhotic patients (10). Forty-one patients developed a small monofocal lesion and had diagnostic evaluation with CT, contrast enhanced Doppler ultrasound and a biopsy, the latter being used as the "golden standard". The accuracy of the imaging techniques for the diagnosis of HCC was 83%, with a sensitivity of 95%, a specificity of 71%, and a positive and negative predictive value of 76% and 94% respectively. Although the biopsy has also its limitations, those results indicate that imaging techniques are not 100% accurate in the diagnosis and characterization of focal liver lesions.

1.5. *The diagnostic value of a percutaneous biopsy of a focal liver lesion*

The results of the different techniques (Fine Needle Aspiration Biopsy FNAB, Fine Needle Cutting Biopsy FNCB, Fine Needle Tru-cut Biopsy FNTCB) will be discussed in detail in section 2. They have been recently reviewed by Michielsen *et al.* and are summarized in table 3 (11). In the Durand series (6), the overall accuracy for the diagnosis of HCC by biopsy was 91% (sensitivity 90%, specificity 100%, positive predictive value 100%, negative predictive value 14%). Localization in the posterior and superior segments (IVb, VII, VIII) was the only independent risk factor for a false negative result. In the Herszenyi series (14) included in the review by Michielsen *et al.* (11), sensitivity was 93% for the diagnosis of malignancy, with a specificity of 100%. Size (< 2 cm), posterosuperior localization and inexperience were identified as risk factors for false negative results.

1.6. *Implications on therapy*

A false negative result can lead to an incorrect diagnosis and staging of malignancy. This can largely influence oncological decision-making, whereby histological evidence is mostly required before a chemotherapeutical protocol can be applied. A false negative result can also delay the application of potential curative treatment such as liver resection or transplantation. False positive results can expose the patients to the risks and inconveniences of an unnecessary treatment.

In the Torzilli series, 221/225 of the initial diagnoses were confirmed, 4 patients out of 160 underwent surgery for what appeared to be a benign lesion not needing surgery (9). In the Durand series, 122/137 patients were diagnosed with HCC before surgery (6). The 15 remaining patients underwent surgery without pre-operative histological confirmation. 13 had their suspicion of hepatocellular carcinoma confirmed, but 2 patients had only a benign nodule. Those patients did not have any serious complication of treatment.

If one wants to establish guidelines for performing biopsy of a focal liver lesion, one has to balance between the risks and implications of both false negative and false positive results.

1.7. *Guidelines*

Until recently much controversy existed regarding the question when to perform a biopsy in case of a focal liver lesion. Vergara *et al.* (8), who reported on cutaneous seeding after a percutaneous Fine Needle Aspiration Biopsy (FNAB) of liver metastases in colon cancer, suggested "using this method for cytological diagnosis in hepatic tumours when surgical resection is not possible and when patients will be treated with invasive therapies and to avoid FNAB in patients undergoing surgical resection or when there is a confident diagnosis of HCC by non-invasive procedures". Stolzel *et al.* (15) confirm, "that in case of lesions highly suspicious for HCC, a biopsy should be performed in case surgical (curative) treatment is no option". Takamori *et al.* (4), who report on a frequency of 5.1% of needle tract seeding in 91 patients with HCC, stated that "percutaneous needle biopsy of suspicious hepatic lesions should not be performed indiscriminately because there is a significant

risk for needle tract implantation. These biopsies should be reserved for those lesions in which no definitive surgical intervention is planned and pathological confrontation is necessary for a non-surgical therapy".

For patients with underlying chronic liver disease, guidelines have recently been worked out at the EASL 2000 conference and reported by Bruix *et al.* (16). According to the reporting experts, "the decision to request a diagnostic biopsy should take into account the clinical impact and the balance between the potential risk of biopsy if using a fine needle and the risk of invasive treatments (i.e. transplantation) in a patient due to false positive diagnosis bases solely on imaging techniques". They insist on the risk of performing surgery or even transplantation for benign lesions when diagnosis is only based on imaging techniques. The guidelines they established are based on the following elements :

1. Tumour growth from an undetectable lesion to 2 cm takes 4 to 12 months.
2. Lesions either hypo- or hyperechogenic on ultrasound and < 1 cm are in 50% of cases not a HCC.
3. Besides cytohistological diagnosis, the diagnosis of HCC can also be made on the basis of the following non-invasive criteria :
   a. Radiological : 2 coincident imaging techniques (ultrasound, spiral CT, MRI and angiography) showing a focal lesion of > 2 cm with arterial hypervascularization,
   b. Combined criteria : one imaging technique showing a focal lesion of > 2 cm with arterial hypervascularization and an alpha foetoprotein (AFP) of > 400 ng/ml.

When a focal liver lesion is discovered – a 6-monthly screening by ultrasound and AFP dosage is recommended in chronic liver diseases and cirrhosis – the following guidelines can be applied :

1. When the lesion measures < 1 cm : follow-up every 3 months until it exceeds 1cm.
2. When the lesion measures ≥ 1 cm and < 2 cm : imaging techniques are not sufficiently accurate to distinguish between HCC and other benign or malignant lesions, and AFP does usually not exceed 400 ng/ml. In these conditions a biopsy is recommended.
3. When the lesion exceeds 2 cm, imaging techniques may accurately establish the diagnosis of a HCC. If so, a biopsy is not required.

If no underlying liver disease is known, a biopsy is not required if there is no clinical suspicion of malignancy and imaging examinations show typical lesions [i.e. haemangioma, follicular nodular hyperplasia (FNH)]. If there is any clinical suspicion and/or if the images are atypical, a biopsy is strongly recommended.

When a biopsy is to be performed following those guidelines, some precautions much be taken. It is evident that contra-indications have to be respected. A 1 cm thickness of covering parenchyma is advised, and the number of passages must be limited. A negative biopsy can never be used as a criterion to rule out malignancy. More false negative results are noted when the lesion is small (< 2 cm) or localized in the posterosuperior segments (IVb, VII, VIII). Surveillance of the puncture site is warranted.

Finally, as the imaging techniques are still evolving and new techniques emerge (i.e. contrast enhanced Doppler ultrasound, harmonic and pulse-inversion harmonic ultrasound) the criteria may change in the future.

2. Fine Needle Aspiration Biopsy (FNAB), Fine Needle Cutting Biopsy (FNCB) or Fine Needle Tru-cut Biopsy (FNTCB)

When a biopsy is indicated according to the criteria, the question raises which technique to use. The biopsies are mostly performed under ultrasound guidance, but can also be performed under CT scan when the lesion is difficult to visualize on echography or according to local expertise. It is now generally accepted that a fine needle (defined as ≥ 19G or ≤ 0.9 mm outer diameter (11,12)) should be used. Larger needles give a better sampling but have more complications and are therefore not suitable.

Essentially 3 fine needle techniques are available :

1. Fine Needle Aspiration Biopsy (FNAB) : a spinal needle is used, with a bevel of varying angulations and without a cutting edge. Aspiration is realized by applying negative pressure with a syringe
2. Fine Needle Cutting Biopsy (FNCB) : a needle is used with a cutting tip with or without bevel, and with an inner stylet preventing fragmentation or distortion of the biopsy by violent aspiration forces (i.e. Surecut®, a modified Menghini Needle)
3. Fine Needle Tru-cut Biopsy (FNTCB) : the needle uses a tru-cut technique : an inner stylet with a side notch is inserted into the lesion, and a cutting sheath is fired forward trapping a tissue sample in the side notch (i.e. Temno Biopty Gun®)

In a review by Michielsen *et al.*, the results of different published series using different techniques have been analyzed and summarized in table 3 (11). As already mentioned, we analyzed at our institution a series of 245 consecutive biopsies (results partially published (11,12,13)) of focal liver lesions by FNTCB using a Temno Biopty Gun® of 21G in patients in whom a definitive diagnosis could be established by autopsy, surgery or a clinical follow-up of at least 6 months. The sensitivity for the diagnosis of malignancy was 86%, the specificity 88% and the accuracy 88%. The positive predictive value was 100%, the negative predictive value, however, was only 56% and the insufficient sampling rate was 2.5%.

In most of the series only one technique was used. In only 8 series 2 techniques were used and partially

compared (11). The following conclusions can be drawn from the available data :

1. Accuracy, sensitivity, specificity, positive and negative predictive value in discriminating benign from malignant lesions are comparable for the 3 techniques. The best results are achieved with a combination of FNAB with a cutting technique. FNAB is less accurate in case of a well-differentiated HCC, a cholangiocarcinoma and a lymphoma.
2. The insufficient sampling rate tends to lower in FNTCB compared to FNCB and more clearly compared to FNAB. In the latest, insufficient sampling is higher in fibrotic lesions, necrotic tumor and vascular tumours.
3. Complication rate is comparable for the true fine needle techniques. Huang *et al.*, however, reported a higher incidence of needle tract seeding in FNCB (3.2%) compared to FNTCB (1.5%) (5).
4. FNCB and FNTCB are superior to FNAB for the histological characterization of the lesion. This is of particular importance in a well-differentiated HCC, in a cholangiocarcinoma, in metastatic disease to give an indication of the nature of the primary tumour, and finally in the characterization of a benign lesion.
5. Experience of the clinician, the pathologist and cytopathologist largely influence these factors.

All these elements should be taken into account when making the choice for the appropriate technique.

3. Elements of cost and cost-effectiveness

In economical evaluations different types of costs are distinguished (17). We will only consider the direct costs : the costs related directly to medical consumption. Indirect costs (due to time loss, unrelated future health costs because of prolonged life time) and intangible costs (costs of pain, anxiety, etc.) are not considered. Cost-effectiveness is about health gains that are measured in one-dimensional natural units (e.g. hospitalizations prevented) and that take only the quantity of an outcome in consideration (if the outcomes are weighted according to their quality and desirability, then the term cost-utility is used). Data on cost-effectiveness are scarce. Beard *et al.* analyzed the cost-effectiveness of hepatic resection for colorectal liver metastases and found a benefit of 1.6 life years at a cost of £6,742 (18). The role of the biopsy was not clearly established in their analysis. Cost-effectiveness of biopsy of a focal liver lesion is very difficult to asses anyhow because the study population is extremely heterogenic, the number of patients in the series is relatively small, there is no standardized treatment in the subgroup with HCC and cirrhosis, and the costs are very different from one country to another. We will therefore focus on the direct costs.

The direct costs of the biopsy are determined by multiple elements : technique and materials used, ultrasound, CT or MRI, the cost for the technical act, inpatient or outpatient procedure, histology versus cytology and the cost of complications.

Table 4. — **Costs of biopsy of a focal liver lesion at our institution**

Material :			
Biopty Gun®	€ 32.53		
Needle for aspiration	€ 1.24		
Other material	€ 5.58		
Technical act :	€ 113.39		
Pathological analysis :			
Biopsy	€ 82.58		
Cytology	€ 49.05		
Inpatient 1 night :	€ 598.10		
Outpatient care :	€ 60.03		
Total costs (€) :			
	FNAB	FNTCB	FNAB+FNTCB
Inpatient	767,36	832,18	882,47
Outpatient	229,29	294,11	344,40

In the paper by Torzilli *et al.* (9), the following costs were enumerated : US guided FNB £266, ultrasound £47, contrast enhanced CT £197, MRI £211 and angiography with lipiodol £254. They also stated that the biopsy on itself was cheaper then the imaging techniques, but in practice however imaging techniques are always performed. In the United States, the cost is estimated at $1030 (19).

The costs at our institution are summarized in table 4. The costs are less when the biopsy is performed on an outpatient base. This, however, is not always justified and criteria have been established and published by Jacobs *et al.* on behalf of the Patient Committee of the American Gastroenterological Association, summarized in table 5 (20). If these criteria are met, biopsy should preferentially be performed on an outpatient base to reduce costs.

Conclusions

Liver biopsy has long time been considered as the golden standard in the characterization of focal liver lesions, although it ensues some complications, such as haemorrhage and needle tract seeding. As the imaging techniques have largely improved their diagnostic accuracy, biopsy is not always indispensable. Criteria have been established for the subgroup of patients with chronic hepatic disease having an increased risk for hepatocellular carcinoma. If according to the criteria a biopsy has to be performed, Fine Needle Tru-cut Biopsy is preferable, according to local expertise. It is superior to cytology of aspiration biopsies to determine the exact nature of the lesions. The cost-effectiveness of the biopsy is difficult to assess, but the direct costs can be calculated. Performing the biopsy on an outpatient base according to the established criteria can substantially reduce costs and should therefore be encouraged.

Table 5. — **Criteria for liver biopsy on an outpatient base by Jacobs *et al.* (20) on behalf of the Patient Care Committee of the American Gastroenterological Association**

Able to return in 30'
Reliable person present during first night
No serious medical problem increasing risk of complications
Hospital requirements :
Approved laboratory
Blood-banking unit
Easily accessible inpatient bed
Monitoring facility for 6 H
Hospitalization if evidence of
Bleeding
Bile leak
Pneumothorax
Other organ puncture
Pain requiring more then 1 dose of analgesics in 1st H

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