Fine needle trucut biopsy in focal liver lesions : a reliable and safe method in identifying the malignant nature of liver lesions

Filip F. De Pauw[1], Sven M. Francque[1], John-Paul J. Bogers[2], Ivo K. Duysburgh[3], Paul A. Pelckmans[1], Eric A. Van Marck[2], Peter P. Michielsen[1]

Divisions of (1) Gastroenterology and (2) Pathology, University Hospital Antwerp, Belgium ; Division of (3) Gastroenterology, Maria Middelares St. Niklaas, Belgium.

Abstract

Background and study aims : **The correct management of a focal liver lesion, suspected of being malignant, requires tissue for histopathological examination. To this purpose an ultrasonically guided fine needle trucut biopsy technique (FNTCB) can be used, to allow obtaining large tissue samples.**

The aim of the study is to see that FNTCB is a reliable method in identifying the malignant or benign character of a focal liver lesion.

Patients and methods : **We retrospectively compared the results of 231 FNTCB of focal liver lesions with the final diagnosis.**

Results : **In 191 lesions a final diagnosis was obtained (164 were malignant, 27 were benign). In our series FNTCB has a sensitivity of 86.6% (142/164), a specificity of 100% (27/27) and an overall accuracy of 88.5% (169/191) in identifying malignancy. There was a correct identification in 79.4% (27/34) of primary liver tumours and 88.5% (115/130) of liver metastases. In 52% (60/115) of liver metastases the primary site was accurately suggested by the pathologist. Correct characterization of benign liver lesions was obtained in 63% (17/27) of the cases. The insufficient sample rate was 3.1% (6/191). In one patient with thrombocytopenia an intraabdominal haemorrhage occurred**

Conclusions : **FNTCB is a reliable and safe method in identifying the malignant nature of liver lesions. Due to the large tissue sample, insufficient sample rate is low and an accurate histological identification of benign lesions, primary liver malignancies and metastases can be made. In case of metastases it is often possible to determine the site of the primary tumour.** (Acta gastroenterol. belg., **2007**, 70, **1-5**).

Key words : liver lesions, fine needle trucut biopsy, ultrasound guidance.

Introduction

Because of the technical improvement and the more wide-spread use of imaging techniques focal liver lesions are more frequently found. For further management of these lesions a correct characterisation is necessary. This is not always possible using only imaging techniques. Other methods like neural networks seem to be promising. Rudzki *et al.* (1) used a neural network with clinical and laboratory input, to predict whether the lesion was benign or malignant. Sensitivity was 94.4%, specificity 98.9% and accuracy 97.1%. However, when obtaining a negative result for malignancy, one is not certain whether there is no malignancy present (and the lesion is truly benign) or the result is false negative (and the malignant lesion is missed) because the lack of histopathological prove.

At this moment pathological (cytological or histological) examination of tissue often remains necessary to obtain a correct diagnosis (2,3). Tissue can be obtained surgically (gold standard) or, in a less invasive and more elegant way, using a fine needle defined as having an outer diameter $\leq$ 0.9 mm or $\geq$ 19G (4). For this means fine needle aspiration biopsy (FNAB) has been proven to be a reliable method. However, we believe that a biopsy using a trucut fine needle (FNTCB), the type of fine needle used in our series, is an equally reliable method in identifying malignancy and has certain advantages.

The aim of the study is is to assess if FNTCB is a reliable method in identifying the malignant or benign character of a focal liver lesion. Further we want to see in how many cases a correct histological diagnosis can be made and, in case of liver metastases, in how many cases the primary site of the tumour can be correctly predicted.

Patients/materials and methods

From August 1990 till February 1999 231 FNTCB of focal liver lesions were performed in 214 consecutive patients (11 patients had 2 biopsies, 3 patients had 3 biopsies) in the department of gastro-enterology and hepatology of the University Hospital Antwerp. The age of the patients varied from 5 to 89 years, with a mean age of 60.6. Ninety nine (55,6%) were male, 79 (44,4%) were female. The biopsies were performed under ultrasound guidance with a 4-or 5-MHz linear puncture transducer (Toshiba Sonolayer SSA-250A). A fine needle (21 Gauge Temno Biopty Gun) was used. This is a semi-automated device with a central stylet with a side notch and an outer cannula with a cutting edge. The needle is introduced into the liver with the tip just in front of the lesion, the central stylet with side notch is advanced into the lesion and by means of a spring-loaded device the outer cannula is fired over the exposed side notch, thus trapping the specimen. The obtained tissue core is then fixed in neutral formalin solution, and

Address for correspondence and requests for reprints : F. De Pauw M.D. and P. Michielsen, M.D., Ph.D., University Hospital Antwerp, Wilrijkstraat 10, B-2560 Edegem, Belgium. E-mail : peter.michielsen@uza.be.

Submission date : 21.11.2006
Acceptance date : 21.12.2006

Table 1. — **Stainings that were used (n = number)**

Classical staining	(n : 485)	Immunohistochemical staining	(n : 176)
Haematoxylin-eosin	191	Pancytokeratin	26
PAS(D)	135	α-foetoprotein	25
Sirius	55	CEA	24
Gordon Sweets	38	Chromogranin	11
Trichrome-Masson	25	Synaptophysin	10
Perls	16	Neuron Specific Enolase	9
Alcian Blue	11	Estrogen receptor	6
Fouchet	6	α1-antitrypsin	6
Grimelius	5	LCA	6
Giemsa	2	Leu7	5
Ziehl Neelsen	1	Progesteron receptor	5
		β-HCG	4
		α1-antichymotrypsin	3
		CA15.3	3
		CA125	3
		Hepatitis B surface- hepatitis B core	3
		S100	3
		PLAP	2
		EMA	2
		HMB45	2
		PSA-PSAP	2
		ACTH	1
		Calcitonin	1
		CK7	1
		CK20	1
		Desmin	1
		Insulin-Pro-insulin	1
		Glucagon	1
		Neurotensin	1
		Pancreatic Polypeptide	1
		Somatostatin	1
		Vimentin	1
		VIP	1
		CD15	1
		CD20	1
		CD31	1
		CD45RO	1

sent to the pathology laboratory. After embedding in paraffin, the tissue is stained with haematoxylin and eosin. Additional histochemical and immunohistochemical stainings are performed if appropriate. Additional stainings are listed in table I.

The results of these biopsies were retrospectively compared with the final diagnosis, obtained by histological examination of material from surgery, endoscopy or autopsy. If this was not available a clinical diagnosis was accepted if there was a follow-up period of at least three months. A part of these cases were already included in another analysis (5). The value of this technique in identifying malignant liver lesions was examined by calculating diagnostic indices. Biopsies in which no final diagnosis was obtained according to the criteria listed above were omitted in these calculations. Diagnostic indices include : sensitivity (percentage of correctly identified proven malignancies), specificity (percentage of biopsies considered to be benign in patients with no malignancy), accuracy (percentage of correctly identified benign and malignant lesions), predictive value of a negative test (percentage of negative biopsies that proved to be benign) and predictive value of a positive test (percentage of biopsies positive for malignancy that proved to be malignant).

When a past history of a malignancy was known, this was given to the pathologist as clinical information.

If the tissue sample was insufficient to allow a histological examination because it was too small or because there was only necrotic tissue, the biopsy result was considered to be negative (no proof of malignancy). The number of fragments, obtained with punction of a lesion (one or more passages in the same session) was counted. The length and width of the largest fragment were also measured. In case of biopsies of malignant lesions we divided the biopsies into two groups (largest fragment smaller than 5 mm and largest fragment larger than or equal to 5 mm) and compared the true positive and false negative between the two groups with a chi-square test. If liver tissue was present, we looked for a liver-tumour interface and the number of portal tracts was counted.

Results

Two hundred thirty one FNTCB were performed. A final diagnosis was obtained in 191 cases, in 132 based on histological examination, in the other 59 cases on clinical grounds. Only the data of these 191 were included in the further analysis. The number of fragments obtained varied from 1 to 10 (mean 2.96). The

Table 2. — **Diagnostic indices**

Diagnostic indices		
Sensitivity	86.6%	89.8%
Specificity	100.0%	100.0%
Accuracy	88.5%	91.4%
Negative predictive value	55.1%	62.8%
Positive predictive value	100.0%	100.0%

Left column : insufficient samples included.
Right column : insufficient samples not taken into account.

mean length of the fragments was 5.3 mm (range 0.3-15.0 mm), the width varied from 0.3 mm to 1.0 mm (mean 0.4 mm). In 123 of the 191 biopsies pre-existing liver tissue was present, in 55 cases a liver-tumour interface was present, the average number of portal tracts in the biopsies with liver tissue was 1.59 (195 in 123 biopsies, range 0-7).

The result of the biopsy was compared with the final diagnosis (table II). Final diagnoses are listed in table III. In our series there was an insufficient sample rate of 3.1% (6/191).

Of 164 malignant lesions, 142 were correctly identified as being malignant, resulting in a sensitivity of 86.6% ; 79.4% (27/34) of the primary liver tumours were correctly characterised (8/9 cholangiocarcinoma, 19/25 hepatocellular carcinoma), as was the case for 88.5% (115/130) of the liver metastases. In 60 of the 115 metastases (52%) the correct primary site was suggested by the pathologist, in another 38 cases (33%) accurate information about the primary tumour was given without an indication of the primary site (e.g. a well differentiated adenocarcinoma), in the other cases (17/115) only a vague description (e.g. cells originating from a large cell tumour) or no further specification (e.g. insufficient malignant cells for further specification) could be given. All benign lesions (27/27) were correctly recognised (specificity 100%). In 17 cases an accurate histological diagnosis was made. In those cases in which histological examination of the biopsy showed aspecific

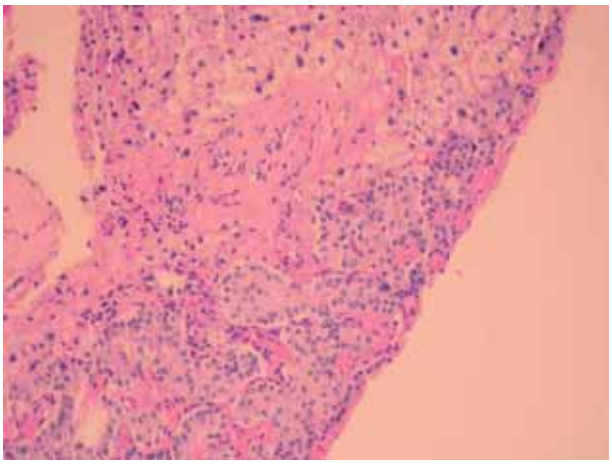

Fig. 1. — Medium-power image of the interface between tumour tissue and normal liver tissue in a patient with a liver metastasis of a neuro-endocrine tumour of the pancreas (PAS-D staining, 20×).

Table 3. — **Final diagnoses (n = number), n.o.s. : not other specified**

Malignant lesions	(n : 122)	Benign lesions	(n : 27)
Primary liver tumours		Steatosis	8
		Abscess	2
Hepatocellular carcinoma	19	Haemangioma	2
Cholangiocarcinoma	9	Focal Nodular Hyperplasia	2
		Regenerative nodule	1
		Lymphangioma	1
Secondary liver tumours		Adenoma	1
		Aspecific lesions	10
Colon	33		
Pancreas	13		
Breast	10		
Stomach	8		
Lung (non-small cell)	5		
Lung (small cell)	4		
Carcinoid	4		
Oesophagus	3		
Kidney	3		
Lymphoma	3		
Neuro-endocrine (n.o.s.)	3		
Ovarium	2		
Gallbladder	2		
Small cell (n.o.s.)	2		
Schwannoma	1		
Germcell	1		
Insulinoma	1		
Endometrium	1		
Leiomyosarcoma	1		
Melanoma	1		
Unknown primary	21		

findings with absence of malignancy, further follow-up revealed no malignancy. Diagnostic indices including accuracy and predictive value for a negative and a positive test result are given in table II, taking into account the insufficient samples. The results that are achieved if the insufficient samples are omitted, which is the case in many other studies, are also listed in table II.

Comparison of true positive and false negative results in malignancy between biopsies whose largest fragment is smaller than 5 millimetres versus those biopsies whose largest fragment is equal to or larger than 5 millimetres showed no significant difference ($p = 0.673$).

In our series only one complication occurred : an intraabdominal haemorrhage in a patient with thrombocytopenia (74.000/mm^3), necessitating a transfusion of 500 ml of packed cells. We observed no case of tumour seeding along the needle tract.

Discussion

FNAB, a technique using a spinal needle, has been used for many years to obtain a tissue sample for anatomopathological diagnosis of a focal liver lesion. According to Fornari *et al.* (6) and confirmed by others (4,7,8,9) this technique has a high sensitivity and specificity in recognising malignancy. Tissue samples are, however, small, often only allowing cytological examination. Furthermore insufficient sample rate is high : in the series of Borzio (10) an insufficient sample rate of 7.5% is reported. Those insufficient samples are not always taken into account calculating diagnostic indices. When they are not omitted, sensitivity and specificity are significantly lower.

FNTCB, the technique used in our series, uses a central stylet and outer cannula as described above and allows obtaining larger tissue samples, resulting in a low insufficient sample rate. Sensitivity, specificity and accuracy are high. Because there are no false positive results (specificity 100%), the predictive value for a positive test result is 100%. The predictive value for a negative test result however is low (55.1%), so if the biopsy is negative for malignancy, we are still in doubt whether the lesion is malignant or not.

Because of larger tissue samples, compared to FNAB, a more thorough histological examination is possible, allowing a more precise diagnosis. Using FNAB, the rate of correctly characterised benign lesions is disappointing (11,12). In our study, in 63% (17/27) of the benign lesions a correct histological diagnosis was made. Obtaining an accurate histological diagnosis of a benign lesion helps to exclude the possibility of a false negative result, thus avoiding a new punction, and allows an appropriate treatment. Concerning secondary malignant lesions, histological examination allowed in 52% (60 out of 115 cases) to correctly predict the primary site of the tumour. In 33% (38 out of 115) additional useful information concerning the primary tumour was given (e.g. a moderately differentiated adenocarcinoma), orientating further search for the primary tumour. The additional information was obtained in some cases from more specific stainings that could be performed thanks to the sample size. Using only cytology, the diagnosis of cholangiocarcinoma and (well-differentiated) hepatocellular carcinoma (13) is often difficult. With the FNTCB, a correct diagnosis of a primary liver tumour was possible in most of the cases.

Immuno-histochemical staining was performed in some hepatocellular carcinomas and, furthermore, in some cases of metastases of an adenocarcinoma or a large cell tumour with unknown primary site to orientate the diagnosis. Immunohistochemistry is now routinely used (14). It has proven to be useful in differentiating well-differentiated hepatocellular carcinomas from benign hepatocellular nodular lesions (14,15). For this purpose αFP, pCEA, CD10, CD34 can be used. Further immunohistochemistry can be used to differentiate between poorly-differentiated hepatocellular carcinoma and cholangiocarcinoma (16,17). Finally histological typing and primary site of a metastatic adenocarcinoma can often be determined (18). In our series, for example, in one patient known with a carcinoma of the prostate a suspicious liver lesion was found on ultrasound. Classical histology and additional staining for PSA and PSAP suggested that there was a second primary tumour. Finally the diagnosis of a pancreas adenocarcinoma was made. Further immunohistochemistry was helpful to make the diagnosis of some types of tumours. In one case a liver metastasis of a neuro-endocrine tumour of the pancreas was found. The presence of insulin and pro-insulin could be shown by immunohistochemical staining in the pancreas lesion, but not in the liver lesion. An in situ-hybridisation for insulin revealed the presence of insulin and pro-insulin in the liver lesion, so the diagnosis of a metastasis of an insulinoma with secretion but without accumulation of insulin could be confirmed. Other diagnoses include schwannoma, lymphoma, carcinoid tumour and melanoma (19). Detection of oestrogen or progesterone receptor in breast carcinoma is also possible, influencing further treatment.

Despite the fact that fine needle biopsy is a (semi-)invasive examination, the complication rate is low. In large multicentric studies major complications (complications necessitating therapy or having sequela) occurred in 0.036% (20) to 0.031% (21) of the biopsies, mortality occurred in 0.006% (22) to 0.0031% (20). Haemorrhage is the most frequent and severest complication. In our series we observed one severe bleeding in a patient with thrombocytopenia. Surgery was not needed, but a blood transfusion was necessary. Especially in highly vascularised lesions (haemangioma, angiosarcoma) severe bleeding can occur. If imaging techniques are suggestive for such a lesion, a punction is relatively contra-indicated. However, by proper selection of patients and careful technique, the risk of significant haemorrhage is very low (23). Tumour seeding along the needle tract, often mentioned in discussions about needle punctions, is a

rare complication using fine needles and performing the puncture by passage through normal liver tissue. Incidences from 0.003 to 0.017% are reported in large multicentric studies (24). There was no case of tumour seeding in our series.

In conclusion, FNTCB is a safe technique with high sensitivity and specificity in identifying malignant liver lesions. Due to the large tissue samples, insufficient sample rate is low and an accurate histological identification of benign lesions, primary liver malignancies and metastases can be made. In the case of metastases it is often possible to determine the site of the primary tumour.

References

1. RUDZKI K., HARTLEB M., SADOKOVSKI T. *et al.* Focal liver disease : neural network-aided diagnosis based on clinical and labotory data. *Gastroenterol. Clin. Biol.*, 1997, **21** : 98-102.
2. REYNAERT H., VAN VLIERBERGHE H., OP DE BEECK B., ROSKAMS T. Management of small focal liver lesions in a cirrhotic liver : discussion. *Acta Gastroenterol. Belg.*, 2006, **69** : 236-7.
3. LEONI S., PISCAGLIA F., RIGHINI R, BOLONDI L. Management of small hepatocellular carcinoma. *Acta Gastroenterol. Belg.*, 2006, **69** : 230-5.
4. HOLM H., TORP-PEDERSEN S., LARSEN T. *et al.* Percutaneous fine-needle biopsy. *Clin. Gastroenterol.*, 1985, **14** : 423-450.
5. DUYSBURGH I., MICHIELSEN P., FIERENS H. *et al.* Fine needle trucut biopsy of focal liver lesions. *Dig. Dis. Sci.*, 1997 , **42** : 2077-2081.
6. FORNARI F., CIVARDI G., CAVANNA L. *et al.* US guided fine-needle aspiration biopsy : a highly diagnostic procedure for hepatic tumors. *Am. J. Gastroenterol.*, 1990, **85** : 1009-1015.
7. DUMAS O., ROGET L., COPPERE H. *et al.* Etude comparée des données de la cytoponction à l'aiguille fine et des aspects échographiques. *Gastroenterol. Clin. Biol.*, 1990, **14** : 67-73.
8. BUSCARINI L., FORNARI F., BOLONDI L. *et al.* Ultrasound guided fine-needle biopsy of focal liver lesions : techniques, diagnostic accuracy and complications. *J. Hepatol.*, 1990, **11** : 344-348.
9. MICHIELSEN P., DUYSBURGH I., FRANCQUE S. *et al.* Ultrasonically guided fine-needle puncture of focal liver lesions : review. *Acta Gastroenterolog. Belg.*, 1998, 158-163.
10. BORZIO M., BORZIO F., MACCHI R. *et al.* The evaluation of fine needle procedures for the diagnosis of focal liver lesions in cirrosis. *J. Hepatol.*, 1994, **20** : 117-121.
11. MONTALI G., SOLBIATI L., CROCE M. *et al.* Fine needle aspiration biopsy of focal liver lesions ultrasonically guided with a real time probe. *Br. J. Radiol.*, 1982, **55** : 717-723.
12. ZORNOZA J., WALLACE S., ORDONEZ N. *et al.* Fine-needle aspiration biopsy of the liver. *Am. J. Radiol.*, 1979, **134** : 331-334.
13. LIMBERG B., HOPKER W., KOMMEREL B. *et al.* Histologic differential diagnosis of focal liver lesions by ultra- sonically guided fine-needle biopsy. *Gut*, 1987, **28** : 237-241.
14. WEE A. Fine needle aspiration biopsy of the liver : algorithmic approach and current issues in the diagnosis of hepatocellular carcinoma. *Cytojournal*, 2005, **2** : 7.
15. STAHL J., VOYVODIC F. Biopsy diagnosis of malignant versus benign liver nodules : new helpful markers. An update. *Adv. Anat. Pathol.*, 2000, **7** (4) : 230-239.
16. LAU S., PRAKASH S., GELLER S. *et al.* Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma and metastatic adenocarcinoma. *Human Pathology*, 2002, **33** : 1175-1181.
17. TSUJI M., KASHIHARA T., TERADA N. *et al.* An immunohistochemical study of hepatic atypical adenomatous hyperplasia, hepatocellular carcinoma, and cholangiocarcinoma with α-fetoprotein, carcinoembryonic antigen, CA19-9, epithelial membrane antigen and cytokeratins 18 and 19. *Pathology International*, 1999, **49** : 310.
18. GUPTA K., KENWRIGHT D., NARAN S. *et al.* Aspiration cytodiagnosis of small cell malignancies found in fine needle aspirate of the liver : an immunocytochemical study. *Cytopathology*, 2000, **11** : 262.
19. VAISBEIN E, FELDMAN R., NASSER M., COHEN H., NASSAR F. Primary lymphoma of liver : a case report and review of literature. *Acta Gastroenterol. Belg.*, 2004, **67** : 361-2.
20. SMITH E. The hazards of fine needle aspiration biopsy. *Ultrasound Med. Biol.*, 1984, **10** : 629-634.
21. FORNARI F., CIVARDI G., CAVANNA L., DI STASI M., ROSSI S., SBOLLI G. *et al.* Complications of US guided fine needle abdominal biopsy. *Scand. J. Gastroenterol.*, 1989, **24** : 949-955.
22. SMITH E. Complications of percutaneous abdominal fine-needle biopy. *Radiology*, 1991, **178** : 253-258.
23. MC GILL D., RAKELA J., ZINSMEISTER A. *et al.* A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology*, 1990, **99** : 1396-1400.
24. ABDELLI N., BOUCHE O., THIEFIN G., RENARD P., FLAMENT J., ZEITOUN P. Essaimage sous-cutané sur le trajet d'une ponction cytologique percutanée à l'aiguille fine d'une métastase hépatique d'un adénocarcinome colique. *Gastroenterol. Clin. Biol.*, 1994, **18** : 652-656.