Acta Oncologica Vol. 33, No. 1, pp. 33–37, 1994

DIAGNOSTICS OF MALIGNANT LYMPHOMAS WITH ULTRASOUND GUIDED 1.2 MM BIOPSY-GUN

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In a retrospective analysis of 129 ultrasound-guided biopsy-gun biopsies (USGB) from patients with known or suspected malignant lymphoma, a histopathological diagnosis was obtained in 101 (78%) instances and no further procedures for histological verification were required. In the 28 cases with initially non-diagnostic results, 14 new USGBs were performed and a diagnosis was obtained in 11. Thus, a total success rate of 87% was achieved. The correct diagnosis was confirmed with either surgery, autopsy, or radiological or clinical follow-ups (median 40 months). The diagnoses were categorised as Hodgkin's disease and high-grade or low-grade non-Hodgkin's lymphoma. Further subtyping of the lymphoma was possible in a few cases only. Immunohistochemistry was utilised only in a minor proportion of the cases (25/129), but refined the diagnosis in several instances. The biopsy-gun method was safe and minor adverse effects were seen in two patients only.

Malignant lymphomas constitute a heterogeneous group of diseases in which the treatment differs considerably between the three major subgroups, viz. Hodgkin's disease (HD), high-grade, and low-grade non-Hodgkin's lymphomas (NHL). Apart from the histopathological subgroup, stage is also of major clinical importance when choosing therapy.

A diagnostic lymph node biopsy is usually easily performed when superficially located nodes are available. If, however, a laparotomy or a thoracotomy has to be done to obtain a correct diagnosis, this has disadvantages, e.g., the risk of complications, the cost, and the delay of the start of therapy entailed by this procedure. Occasionally, there may also be problems in performing a surgical biopsy from a peripheral site, e.g., when the tumour is close to large vessels or the tissue is fibrotic after previous surgery or radiotherapy.

As an alternative to surgical biopsies, percutaneous needle biopsy guided by ultrasound (US) (1) or computerized tomography (CT) (2), is a well-documented method which can reduce the frequency of surgical biopsies (3, 4). The size of the needles has varied from thin (0.6–0.9 mm) to large (1.3–2.0 mm). A thin needle usually gives aspiration biopsy material for cytological examination, whereas the larger ones provide a cord biopsy for histological examination. The thinner needles give insufficient amounts of material to give a view of the tumour growth architecture (5), and has less diagnostic accuracy in lymphomas than in metastatic cancer (6). The frequency of complications depends on the size of the needle (7) and hence one has to balance the need for sufficient amounts of material for diagnostic purposes with the possible risk of complications.

The use of US-guided biopsy-gun biopsies has been described previously and is reported to achieve good diagnostic accuracy in pancreatic (8) and neuroendocrine tumours (9). The aim of the present retrospective study was to evaluate the diagnostic rate of biopsy-gun biopsies in patients with verified or suspected malignant lymphohmas and the frequency of complications.

Received 21 April 1993.
Accepted 24 October 1993.
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 ISSN 0284-186X

Material and Methods

Patients. Between January 1987 and February 1990, 129 ultrasound-guided biopsy-gun biopsies (USGB) (1.2 mm, Biopty-Cut; C.R. Bard, Covington, GA) were performed in 107 patients with known or suspected malignant lymphoma, using a method earlier described (10). The age of the patients (64 males and 43 females) ranged from 3 to 92 years (median 53 years). Ten patients were biopsied twice, 3 patients 3 times, and 2 patients were biopsied 4 times. In patients who had undergone two or more USGBs, the biopsies were performed at different sites and/or on different occasions. Apart from the 129 primary USGBs, 14 biopsies were performed when the first USGB was inconclusive. These 14 cases are referred to in the text as 're-biopsied'. No specific pre-biopsy tests were required and the patients were asked to remain in bed for 4 h after the biopsy. The USGB was considered conclusive when either a true positive or a true negative result was obtained, and inconclusive if the material was not representative, if the material was not representative, if there was an insufficient amount of biopsy material, if further investigations for histological verification were needed, or if the diagnosis was incorrect. The correct diagnosis was confirmed with either surgical biopsy, autopsy or radiological or clinical follow-up of living patients (median follow-up time 40 months, range 21–59 months).

Histopathology. The biopsies arrived in fresh state to the Department of Pathology. In most instances, all the material was fixed in neutral buffered formalin for routine histopathology (haematoxylin-eosin, Giemsa, PAS, and Laidlaw stains). In 25 cases, sections of the biopsies were snap frozen to −70°C for future immunohistochemical stainings.

Clinical groups. The 129 cases were divided into two groups: New patients with clinically suspected malignant lymphoma (54 USGB); and patients with previously known malignant lymphoma, where the biopsy was taken for the purposes of a) staging (13 USGB), b) evaluating residual tumour mass after treatment (21 USGB), c) verifying a suspected relapse (25 USGB), or d) confirming a suspected transformation of a previously low-grade NHL into a high-grade one (16 USGB).

Regions of biopsy. The regions from where the biopsies were taken were the following; liver (12 USGB), spleen (14 USGB), abdomen and retroperitoneum (62 USGB), mediastinum (10 USGB), and superficial lymph nodes such as the groin or the neck (31 USGB). The latter were performed when the node was located close to large vessels or after previous surgery, when a surgical biopsy would entail an increased risk of complications.

Results

One hundred and one of the 129 biopsies (78%) were conclusive, and no further investigation was needed for histological verification. No false positive result was detected. Twenty-eight of the 129 USGB (22%) were inconclusive. In these cases, 14 re-biopsies were performed and of these 11 were conclusive. Thus, the overall success rate was 112 of the 129 biopsies (87%) (Table 1).

Clinically suspected malignant lymphoma (group 1). In the group of patients investigated for a suspected lymphoma, 33 of 54 USGB (61%) were conclusive (Table 2). In 10 cases a re-biopsy was performed, and 7 of these were conclusive. The total success rate was thus 74%. The lymphoma diagnoses were confirmed with surgical biopsy in 11 cases, at autopsy in 5 cases, and with additional immunohistochemical analysis in 9 cases. In 15 cases, the diagnoses were confirmed by clinical follow-up either at death or after a median follow-up time of 41 months (range 29–59). Of the 8 patients, that were demonstrated to have HD, 3 USGBs were false negative (38%). In two patients, the diagnosis was confirmed by means of laparotomy and in one patient with mediastinoscopy. One of the 5 cases, where the HD diagnosis was based on the USGB, was subgrouped as nodular sclerosis. The other cases were designated as 'HD unclassifiable'. Of the 11 patients who ultimately turned out to have high-grade NHL, 6 were initially positive (55%). After a re-biopsy, 9 (82%) were conclusive. Only 2 of the high-grade NHL were sub-

Table 1

The method of diagnosis in relation to final diagnosis. Number of patients (percent)

Final diagnosis	Total	USGB			Laparotomy/ mediastino-scopy	Other surgical biopsy	Other*
		First	Second	Total			
Malignant lymphomas	78	58	7	65 (83)	7	3	3
Other malignancy	15	13		13 (87)	1		1
Benign lesion	36	30	4	34 (94)		2	
All	129	101	11	112 (87)	8	5	4

USGB = Ultrasound-guided coarse-needle biopsy
* = Autopsy or response to treatment.

Table 2

Patients (in percentage) with conclusive USGB in relation to diagnosis of 54 unknown tumours, clinically suspected to be malignant lymphomas (group 1)

Diagnosis	Total	USGB		
		First	Second	Total
Hodgkin's disease	8	5		5 (62)
Low-grade NHL	10	3	2	5 (50)
High-grade NHL	11	6	3	9 (82)
Other malignancy	15	13		13 (87)
Benign lesion	10	6	2	8 (80)
Total	54	33	7	40 (74)

grouped according to the Kiel-classification, one as lymphoblastic and one as large cell anaplastic, whereas 9 cases were designated 'unclassified high-grade NHL'. Ten patients turned out to have a low-grade NHL but only 3 were diagnosed after the first USGB. After a second biopsy, a total of 5 (50%) could be properly diagnosed. In only 2 of the 5 biopsies subgrouping was performed (both were follicular centroblastic-centrocytic lymphoma).

Previously known malignant lymphoma (group 2). For staging purposes (group 2a), 11 USGB (85%) were conclusive (Table 3). In 7 of these, the biopsy showed malignant lymphoma, and in 4 cases a true negative result was obtained. The true negative results were confirmed at autopsy in two cases, at laparotomy in one case and after a 43-month follow-up time in one case. Two false negative examinations were revealed, one confirmed at surgery and one at follow-up. In cases of residual masses following treatment (group 2b), 20 of 21 USGB (95%) were conclusive. Thirteen cases were true negative, i.e. the patient was in CR, and 7 true positive, i.e. remaining malignant lymphoma was present. One of the biopsies was not possible to analyse due to extensive necrosis, and a second-biopsy showed normal lymphoid tissue and the patient was thus considered to be in CR. Among the 14 patients considered to be in CR, 3 patients relapsed after 10, 13 and 18 months respectively, but not in the regions where the biopsies were taken. The remaining 11 patients have a median follow-up time of 40 months (range 24–59 months). In cases of suspicious relapse (group 2c), 21 out of 25 USGB (84%) were conclusive. Of these, 13 biopsies verified a relapse, i.e. they were true positive. Of the 4 initially inconclusive biopsies, 3 became positive after a re-biopsy. Thus, a total of 24 out of 25 USGB (96%) were conclusive. In one patient, treatment was started despite a negative biopsy and the recurrence was indirectly confirmed since response to treatment occurred. In 8 cases, no malignant lymphoma was found. Two patients relapsed, 7 and 11 months respectively after the biopsy. Once again the relapses did not occur in the same region as the biopsy. The remaining 6 patients have a median follow-up time of 38 months (range 24–40 months). When a transformation of a low-grade NHL to high-grade NHL was suspected (group 2d), all 16 (100%) biopsies were conclusive. Eleven biopsies were true negative, i.e. no transformation was observed. Nine of those patients have died, 8 with low-grade NHL and one after transformation into high-grade NHL, 6 months after the biopsy. Only in one patient was an autopsy carried out. Two patients are still alive with low-grade NHLs after 53 and 59 months respectively. Five of the biopsies were true positive, i.e. they revealed a transformation into a high-grade NHL. In the entire second group, a conclusive diagnosis was obtained in 68 of 75 cases (91%), and if the second biopsy was also included, the success rate was 72 of 75 USGB (96%).

Region of biopsy. The proportions of conclusive biopsies were lower in the spleen (64%) and mediastinum (50%)

Table 3

Patients (in percentage) with conclusive USGB in patients with previously known malignant lymphoma (group 2)

Group	Total	USGB								
		First				Second				Total
		HD	L	H	B	HD	L	H	B	
Staging (2a)	13		2	5	4					11 (85)
Residual tumour (2b)	21	1	5	1	13				1	21 (100)
Relapse (2c)	25	5	3	5	8	2			1	24 (96)
Transformation (2d)	16		11	5*						16 (100)
All	75	6	21	16	25	2			2	72 (96)

HD = Hodgkin's disease
L = Low-grade NHL
H = High-grade NHL
B = Benign
* = transformed low-grade NHL

Table 4

Patients (in percentage) with conclusive USGB in relation to region of biopsy

	Total	USGB						
		First			Second			Total
		LY	M	B	LY	M	B	
Liver	12	3	3	3	1		1	11 (92)
Spleen	14	4		5			1	10 (71)
Mediastinum	10	2	1	2	2		1	8 (80)
Abdomen	62	31	6	14	3		1	55 (89)
Superficial lymphnode	31	18	3	6	1			28 (90)
All	129	58	13	30	7		4	112 (87)

LY = Malignant lymphomas
M = Other malignancy
B = Benign or normal

than in the other regions (range from 75% to 87%) (Table 4). These differences also remained after re-biopsies.

Immunohistochemistry. In 25 cases an immunohistochemical analysis of the biopsy material was attempted and in 19 of these, the biopsy material was sufficient for the analysis. In 12 of these, the diagnosis was refined, and in 6, the analysis confirmed the histopathological diagnosis. In one case, the immunohistochemical analysis did not disclose a high-grade NHL (nor did routine histopathology) after the first USGB, but did so after the second one. In 6 cases it was possible to subgroup the malignant lymphoma only when the results of the immunohistochemical analysis were available.

Complications. Adverse effects were reported in 2 cases. A 92-year-old man with high-grade NHL and an enlarged lymph node behind the urinary bladder was investigated for staging purposes. Immediately after the biopsy, the patient complained of pain in the lower abdomen and his blood pressure fell for a short time, probably as a result of a vasovagal reaction. A transient urinary tract obstruction, probably due to the pain, developed. In the second case, a 65-year-old man, previously treated for high-grade NHL, underwent a spleen biopsy due to a suspected relapse. After the biopsy, he experienced transient abdominal pain lasting for 2–3 h. Repeated US examinations did not reveal any bleeding.

Discussion

The present study showed that a clinically important question as to a patient with suspected malignant lymphoma could be answered by performing one or two USGBs which had a total success rate of 87%. The safety of the procedure was also high, in accordance with reports using CT-guided biopsies (7, 11). In contrast, the use of a slightly larger needle (14–17 gauge) entailed 2 serious complications among 86 biopsies performed (12).

The present positive experience confirms those of other studies, although some of them included a low number of cases or were performed with thinner needles, which provide less material for histological investigation (13–15). The general experience is that larger needles usually provide sufficient material, whereas this is not always the case with thinner needles (12, 16). In one study that compared fine and coarse needles, the accuracy was also very dependent on the experience of the cytopathologist (12).

The 'intermediate-sized' needles used in this study did not usually provide sufficient material for appropriate subtyping of the lymphoma. However, all the biopsies were performed in the daily routine and no attempts were made to re-evaluate the material to increase the proportion of cases where subtyping was possible. The figures represent a clinical routine in which all the diagnoses were made by one haematopathologist. A higher success rate could most likely have been achieved if immunohistochemisty had been performed more frequently (17, 18). Although the difficulties involved with subtyping may not be detrimental for the individual patient with, for instance, a low-grade NHL or HD, since staging and treatment are not affected, they may cause difficulties when a comparison with other studies is necessary. In high-grade NHL it is, however, important to identify lymphoblastic lymphomas since treatment at present differs compared with the other high-grade NHLs.

Due to the proximity of the lungs and great vessels, a US-guided biopsy may be difficult to obtain from the mediastinum. The diagnostic yield was also comparatively low and similar to that reported for fine needles biopsy (11/26 accurate) (19), and biopsy with larger needles (4/6 accurate) (20). In another study, using the same US-guided biopsy-gun method, a high success rate (27/28) was obtained in patients with tumour in the anterior mediastinum (21).

The usefulness of US-guided fine-needle biopsy has been documented in abdominal lymphomas in AIDS patients

(22), in pancreatic lymphomas (23), and in hepatic lymphomas (24). An exception seems to be the spleen, but good experiences have been reported, if the infiltration can be visualised with US (25).

Fewer conclusive biopsies were seen in patients in the initial diagnostic setting (group 1) if compared with cases where a lymphoma diagnosis had already been obtained. A similar experience was reported for fine-needle aspiration cytology (3). For the primary diagnosis, the difficulties appear to be higher in patients with low-grade NHL compared with high-grade NHL and HD, most probably because the diagnosis of low-grade NHL is more dependent on architectural than cellular changes (26).

In HD, the characteristic malignant cells only constitute a minority of the infiltrating cells. For this reason, one would expect an inferior success rate. HD is considered difficult to diagnose by means of aspiration cytology (27) and the diagnostic success is not enhanced by immunocytochemistry (28). A similar difficulty to diagnose HD was not observed in the present study when the results of a second biopsy were taken into account, although the number of cases was limited. The larger amount of material obtained with our needle might explain the apparently higher success rate compared with the fine-needle aspiration biopsy method.

In conclusion, the USGB method is safe and has a high success rate. This makes the need for surgical interventions less frequent. It is also rapidly performed and there is no need for any patient couvalescence. It also seems worthwhile to perform a re-biopsy in cases when the first biopsy does not provide a conclusive diagnosis.

REFERENCES

1. Holm H, Pedersen J, Kristensen J, Rasmussen S, Hancke S, Jensen F. Ultrasonically guided percutaneous puncture. Radiol Clin North Am 1975; 13: 493–503.
2. Zornoza J, Bernardino M, Ordonez N, Thomas J, Cohen M. Percutaneous needle biopsy of soft tissue tumors guided by ultrasound and computed tomography. Skeletal Radiol 1982; 9: 33–6.
3. Pontifex AH, Klimo P. Application of aspiration biopsy cytology to lymphomas. Cancer 1984; 53: 553–6.
4. Wotherspoon A, Norton A, Lees W, Shaw P, Isaacson P. Diagnostic fine needle core biopsy of deep lymph nodes in patients unfit for surgery. J Pathol 1989; 158: 115–121.
5. Haaga J, Lipuma J, Bryan P, Balsara V, Cohen A. Clinical comparison of small- and large-caliber cutting needles for biopsy. Radiology 1983; 146: 665–7.
6. Martelli G, Pilotti S, Lepera P, et al. Fine needle aspiration cytology in superficial lymphnodes: an analysis of 266 cases. Eur J Surg Oncol 1989; 15: 13–6.
7. Welch TJ, Sheedy II PF, Johnson DC, Johnson MC, Stephens DH. CT-guided biopsy: prospective analysis of 1 000 procedures. Radiology 1989; 171: 493–6.
8. Elvin A, Andersson T, Scheibenpflug L, Lindgren PG. Biopsy of the pancreas with a biopsy gun. Radiology 1990; 176: 677–9.
9. Andersson T, Eriksson B, Lindgren PG, Wilander E, Öberg K. Percutaneous ultrasound guided biopsy from liver metastases of endocrine gastrointestinal tumors. Ann Surg 1987; 206: 728–32.
10. Lindgren PG. Percutaneous needle biopsy—A new technique. Acta Radiol Diagn 1982; 23: 653–6.
11. Pagani JJ, Biopsy of focal hepatic lesions. Comparison of 18 and 22 gauge needles. Radiology 1983; 147: 673–5.
12. Binder T, Swobodnik W, Wechsler JG, et al. Sonographisch gefuhrte Fein- und Grossnadelpunktion im abdominalen und retroperitonealen Raum. Dtsch Med Wochenschr 1987; 113: 43–8.
13. Buscarini L, Cavanna L, Fornari F, et al. Ultrasonically guided fine-needle biopsy: A new useful technique in pathological staging of malignant lymphoma. Acta Haemat 1985; 73: 150–2.
14. Erwin BC, Bryness RK, Chan WC, et al. Percutaneous needle biopsy in the diagnosis and classification of lymphoma. Cancer 1986; 57: 1074–8.
15. Tikkakoski T, Siniluoto T, Ollikainen A, Päivänsalo M, Lohela P, Apaja-Sarkinen M. Ultra-sound guided aspiration cytology of enlarged lymph nodes. Acta Radiol 1991; 32: 53–6.
16. Knelson M, Haaga J, Lazarus H, Ghosh C, Abdul-Karim F, Sorenson K. Computed tomography-guided retroperitoneal biopsies. J Clin Oncol 1989; 7: 1169–73.
17. Flens M, van der Valk P, Tadema T, et al. The contribution of immunocytochemistry in diagnostic cytology. Cancer 1990; 65: 2704–11.
18. Robey SS, Clafferty LL, Beschorner WE, Gupta PK. Value of lymphocyte marker studies in diagnostic cytopathology. Acta Cytol 1987; 31: 453–9.
19. Herman SJ, Holub RV, Weisbrod GL, Chamberlain DW. Anterior mediastinal masses: Utility of transthoracic needle biopsy. Radiology 1991; 180: 167–70.
20. Wernecke K, Vassallo P, Peters PE, von Bassewitz DB. Mediastinal tumors: biopsy under US guidance. Radiology 1989; 172: 473–6.
21. Andersson T, Lindgren PG, Elvin A. Ultrasound guided tumour biopsy in the anterior mediastinum. An alternative to thoracotomy and medianstinoscopy. Acta Radiol (in press).
22. Townsend RR, Laing FC, Jeffrey RB Jr, Bottles K. Abdominal lymphoma in AIDS: evaluation with US. Radiology 1989; 171: 719–24.
23. Webb TH, Lillemoe KD, Pitt HA, Jones RJ, Cameron JL. Pancreatic lymphoma. Is surgery mandatory for diagnosis or treatment? Ann Surg 1989; 209: 25–30.
24. Cavanna L, Di Stasi M, Fornari F, et al. Ultrasound and ultrasonically guided biopsy in hepatic lymphoma. Eur J Cancer Clin Oncol 1987; 23: 323–6.
25. Lindgren PG, Hagberg H, Eriksson B, Glimelius B, Magnusson A, Sundström C. Excision biopsy of the spleen by ultrasonic guidance. Br J Radiol 1985; 58: 853–7.
26. Lennert K. Histopathology in lymphomas. 2nd edn. Lennert K, ed. New York: Springer Verlag, 1981.
27. Cafferty L, Ruth K, Nelson O, Cesar C, Fernando C. Fine needle aspiration diagnosis of intraabdominal and retroperitoneal lymphomas by a morphologic and immunocytochemical approach. Cancer 1990; 65: 72–7.
28. Oertel J, Oertel B, Kastner M, Lobeck H, Huhn D. The value of immunocytochemical staining of lymph node aspirates in diagnostic cytology. Br J Haematol 1988; 70: 307–16.