

Value of Ultrasound-Guided Core Biopsy in the Diagnosis of Malignant Lymphoma

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ABSTRACT: *Purpose.* Ultrasound-guided core needle biopsy for the diagnosis and management of malignant lymphomas is controversial and has not been accepted as an alternative to surgical biopsy. We investigate the clinical usefulness of this procedure in a large series of patients.

Methods. Over a 5-year period (2000–2004), ultrasound-guided core needle biopsies were performed in 102 malignant lymphomas. Five diagnostic categories were considered: large B-cell lymphomas (LBCL), small B-cell lymphomas (SBCL), Hodgkin's disease (HD), T cell lymphomas, and miscellaneous. Surgical excisional biopsy of the node was performed in 47 cases (46.1%) for diagnostic confirmation.

Results. The overall diagnostic accuracy of ultrasound-guided core needle biopsy was 88.2% (90/102). SBCL (39), LBCL (36), HD (15), T cell lymphomas (5), and miscellaneous (7) [including T cell–rich B cell (2), natural killer cell (1), Burkitt's lymphoma (1), and non-Hodgkin's lymphoma of the B cell type, NOS (3)] were correctly diagnosed. Three HDs, 1 natural killer cell lymphoma, 1 follicular lymphoma, and 1 LBCL were not correctly diagnosed. The core needle biopsy did not yield tumor tissue in 6 cases.

Conclusions. Ultrasound-guided core needle biopsy is effective in the diagnosis of malignant lymphomas and can be used as the first diagnostic approach in selected clinical situations. © 2007 Wiley Periodicals, Inc. *J Clin Ultrasound* **35**:295–301, 2007; Published online in Wiley InterScience (www.interscience. wiley.com). DOI: 10.1002/jcu.20383

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I mage-guided core needle biopsy has become an important tool in the diagnosis of superficial and deep masses and can frequently avoid the need for open biopsy.¹⁻³ However, it has not gained general acceptance in the diagnosis of malignant lymphoma in lymph nodes because the diagnosis and subtyping of these neoplasms may be limited by the small size of the specimen.⁴

The first trials to diagnose malignant lymphoma using core needle biopsy (CB) were reported 2 decades ago.^{5–7} At the same time, fine needle aspiration cytology procedures were also implemented with similar objectives^{8–11} as the cytologic diagnosis benefitted from flow cytometry techniques.^{12–14} Although the diagnostic accuracy of these techniques is high, traditional lymph node excisional biopsy is still considered by most pathologists as the method of choice in diagnosing malignant lymphomas. Several authors have reported excellent results with image-guided CB of malignant lymphoma.^{5–7,15–26}

We present the results of ultrasound-guided CB in a prospective series of 102 malignant lymphomas.

MATERIAL AND METHODS

At our institution, imaging-guided CBs are routinely performed as a diagnostic approach to deep and superficial tumor masses. During a 5-year period (2000–2004), a total of 294 lymph nodes were biopsied under ultrasound guidance, 79 of them being malignant lymphomas, 113 nonlymphoid malignancies, and 102 reactive/inflammatory diseases. In the same period, the spleen was biopsied in 13 cases, 7 of which were malignant lymphomas. The series also includes 16 malignant lymphomas affecting various extranodal sites, including the liver (4 cases), kidney (2 cases), and

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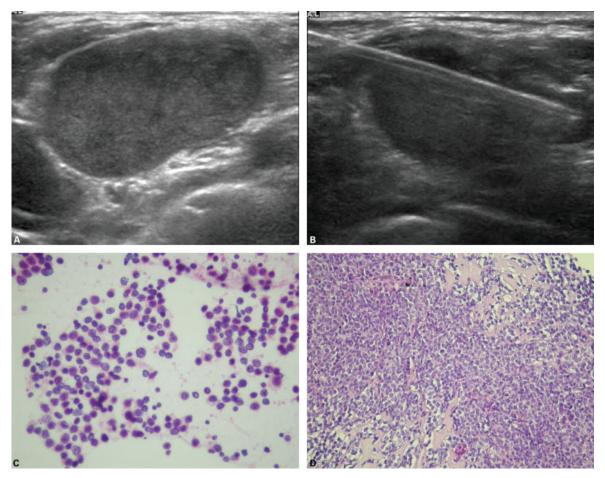


FIGURE 1. A 70-year-old female with a follicular lymphoma. (A) Sonogram shows a supraclavicular node. (B) Sonogram obtained during the ultrasound-guided core biopsy shows the brightly echogenic needle through the node. (C) Cytologic imprint shows a monotonous small-sized lymphoid cell population. (D) Histologic detail of small lymphoid cells showing scarce cytoplasm and hyperchromatic nuclei arranged in a diffuse pattern of growth.

bowel (1 case). Most cases of malignant lymphomas were referred from the hematology clinic. The study was prospective, and the work-up included a detailed clinical history and complete imaging studies (sonography, CT, and MRI when needed) for all patients.

Procedures were performed using a freehand technique in all cases. A 4-7-MHz linear transducer connected o an ATL 3000 or ATL 5000 scanner (Philips Ultrasound 3000, Bothell, WA) was used to guide the puncture in lesions located in the head and neck, axilla, thorax, breast, groin, and extremities (Figure 1A). When the lesion was located in the abdomen or pelvis, a 2–5-MHz convex array probe was used. After local anesthesia with 1% lidocaine, the biopsies were taken using an 18-gauge BioPince needle (Inter-V, Gainesville, FL). The biopsy device offers the possibility to select one of 3 different excursions of the needle ranging from 1.3 to 3.3 cm. The longest possible throw that matched with the target size was selected in every case (Figure 1B). When

the target was an adenopathy and a lymphoma was clinically suspected, 4 to 5 specimens were usually obtained trying to avoid the lymph node's hilium. When other organs were biopsied, the needle was preferably directed at the periphery of the lesion, avoiding central areas, which are frequently necrotic. The gun was always fired when the point of the needle was placed outside but close to the boundaries of the lesion in an attempt to include the capsule in the specimen. Sonography was used to verify the correct placement of the needle through the target lesion.

The obtained tissue fragments were immediately immersed in cooled saline serum to delay cellular autolysis, and then forwarded to the pathology department for processing. The receiving pathologist performed several imprints, and the saline solution was centrifuged. Imprints were stained with hematoxylin-eosin and the centrifugate stained with Papanicolaou stain. Some unstained slides were stored in alcohol for immunohistochemical studies, when needed. Tissue cores were processed using routine techniques. In selected cases, formalin-fixed, paraffin-embedded material was retrieved for molecular analysis [IgH, TcR, and t(14;18) MBR and JH regions].

Lymph node surgical excision was performed in 47 cases (46.1%). In the 55 cases in which surgery was not possible or not needed, the definitive diagnosis was based on hematologic studies, clinical course, previous history, and CB findings.

RESULTS

There was a male predominance in the series (65 males, 37 females) with a mean \pm SD age of 70 \pm 20 years (range, 17–100 years). Location of lesions and diagnostic categories are summarized in Table 1. Malignant lymphomas involved lymph nodes in 79 cases and presented as visceral masses in 23 cases, 7 of which were in the spleen. Head and neck (31 cases) and the axilla and groin (16 and 14 cases, respectively) were most commonly affected, with the extremities being very rarely involved with lymphoma.

No major complications were observed after CB. Minor hematomas and local pain were occasionally reported, but they resolved spontaneously. Post-CB necrosis was found in a splenic mass but was not directly related to the procedure. Malignant seeding along the needle tract was not detected.

The diagnostic work-up involved cytologic, histologic, and immunohistochemical studies in all cases. Molecular studies were performed in 11 cases. Imprints and cytocentrifugates showed crushing artifacts in lymphoid cells. However, they were helpful in cases of suboptimal histopathologic slides. Overall, the diagnostic accuracy of CB in the diagnosis of malignant lymphoma was 88.2% (90/102). There were no false positive cases in the series. Discordant diagnoses are listed in Table 2. Three cases of Hodgkin's disease, 1 natural killer (NK) cell lymphoma, 1 follicular lymphoma, and 1 large B cell lymphoma were not correctly diagnosed. Additionally, the diagnosis could not be made in 6 cases due to the fact that the involved lymph node areas were not adequately sampled by the radiologist. Interestingly, all the discordant cases were located superficially in the neck, axilla, or groin, and most of them (9 out of 12) occurred in the first 2 years of the study.

Small B Cell Lymphoma (39 Cases)

For this type of lymphoma, correlation with surgical/excisional specimens was available in 13 cases (33.3%). Lymph nodes from the head and

TABLE 1
Clinicopathologic Data in 102 Cases of Malignant
Lymphoma Diagnosed on Ultrasound-Guided Core
Needle Biopsy

	n (%)
Organ involved	
Lymph nodes	79 (77.5)
Spleen	7 (6.8)
Extranodal	16 (15.7)
Location	
Head and neck (including supraclavicular fossa)	31 (30.4)
Axilla	16 (15.6)
Groin	14 (13.7)
Viscera	14 (13.7)
Spleen	7
Liver	4
Kidney	2
Bowel	1
Abdomen (extravisceral)	11 (10.8)
Thorax (including breast)	6 (5.9)
Pelvis	2 (1.9)
Extremities	1 (0.9)
Diagnostic categories	
Small B cell lymphoma	39 (38.2)
Large B cell lymphoma	36 (35.3)
Hodgkin's disease	15 (14.7)
T cell lymphoma	5 (4.9)
Others	7 (6.9)

neck, including supraclavicular area, were the most frequently affected (11 cases). Other locations included the groin (6 cases), axilla (5 cases), retroperitoneum (4 cases), abdomen (3 cases), and pelvis, kidney, and breast (1 case each). Salivary glands (parotid and submaxillary) were specifically affected by this category of lymphomas (6 cases).

Follicular lymphomas amounted to 28 cases (71.8%), grade 1 cases being the most common subgroup. Typical cytology and histology and B cell lineage immunohistochemical markers were invariably present. In addition, the double bcl-2/bcl-6-positive immunostaining specifically defined this subcategory. t(14;18) was positive in 6 cases and negative in 5 cases in the molecular analysis. A total of 7 cases were diagnosed as small B cell lymphoma, NOS, one of them showing positive IgH rearrangement. Chronic lymphocytic lymphoma/leukemia was diagnosed in 3 cases (CD5 and CD23 positivity), and MALT lymphoma was diagnosed in 1 case.

Artifacts were not particularly important in this category, and imprints and cytocentrifugates displayed with precision the nuclear characteristics in most cases. The histopathologic diagnosis in this group could not be obtained in 4 cases. The radiologist obtained nondiagnostic material in 3 cases. Only one case of follicular lymphoma was erroneously diagnosed as follicular hyperplasia by the pathologist due to the scarcity of the

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Case	Age/Sex	Location	CB Diagnosis	Final Diagnosis	Discordance
1	48/M	Groin	Nonspecific changes	Follicular NHL, grade 1	Inadequate material
2	17/M	Neck	Nonspecific changes	HD, nodular sclerosis	Inadequate material
3	72/F	Axilla	Nonspecific changes	LBCL	Inadequate material
4	65/M	Axilla	Necrotic tissue	LBCL	Insufficient sampling
5	56/F	Groin	Benign tissue, NOS	T-cell rich B-cell NHL	Inadequate material
6	79/F	Neck	Benign tissue, NOS	Follicular NHL, grade 1	Inadequate material
7	81/M	Axilla	Lymphoid proliferation	NK cell lymphoma	Insufficient sampling
8	40/M	Groin	Reactive/lymphoma	HD, mixed cellularity	Insufficient sampling
9	59/M	Groin	Benign tissue, NOS	Follicular NHL, grade 2	Inadequate material
10	48/M	Axilla	Lymphoid proliferation	HD-LPN	Insufficient sampling
11	50/M	Neck	B cell lymphoma	HD, nodular sclerosis	Insufficient sampling
12	47/M	Groin	Lymphoid hyperplasia	Follicular NHL, grade 1	Insufficient sampling

TABLE 2 Diagnostic Discrepancies in CB Diagnosis of Malignant Lymphoma (12 Cases)

Abbreviations: HD, Hodgkin's disease; HD-LPN, Hodgkin's disease, lymphocytic predominance, nodular type; LBCL, large B cell lymphoma; NHL, non-Hodgkin's lymphoma, NK, natural killer.

material obtained, which made a complete immunohistochemical study impossible. The diagnostic accuracy in this group was 89.7%.

Large B Cell Lymphoma (36 Cases)

For this group of lymphomas, correlation with surgical/excisional specimens was available in 16 cases (44.4%). Lymph nodes in the abdomen (7 cases) and head and neck (6 cases) were the most commonly affected. Other locations included the axilla (5 cases), groin (3 cases), thorax (2 cases), retroperitoneum (2 cases), and breast and arm (1 case each). Interestingly, more than half of lymphomas with viscera in our series (9 out of 14, 64.3%) belonged to this category. Among them, spleen (6 cases), liver (2 cases), and kidney (1 case) involvement were seen.

CBs showed a diffuse lymphoid infiltrate composed of large cells with round nuclei and one or more nucleoli, as expected in this subtype of lymphomas. When the lymphoma involved a viscera, its normal histology could be recognized in some areas, sometimes intermingled with the neoplastic lymphoid infiltrate. B cell lineage markers were positive in all cases. Artifacts were seen at the periphery of cores, and cell morphology and immunostaining in these areas had to be evaluated with caution.

The diagnostic accuracy of CB in this group was 94.6%. In fact, the correct diagnosis could not be reached in only 2 cases. The radiologist obtained inadequate material in 1 case, and the pathologist found extensive necrosis in another.

Hodgkin's Disease (15 Cases)

Correlation with excisional biopsy specimens was available in 7 cases (47%). Nodular sclerosis (6 cases), mixed cellularity (4 cases), and nodular lymphocytic predominance (1 case) subtypes were found. The specific subtype could not be identified in 4 cases due to the fact that the excisional biopsy was not performed in these cases.

The diagnostic accuracy in this group was 73.4% (Table 2). The diagnosis of Hodgkin's disease greatly depends on the identification of typical Reed-Sternberg cells, which is a problem when evaluating small tissue fragments such as cores.

T Cell Lymphoma (5 Cases)

Correlation with excisional biopsy material ws available in 4 cases (80%). Aside from the liver (2 cases), lymph nodes in the axilla, groin, and thorax (1 case each) were involved. There were 4 cases of peripheral T cell lymphoma and 1 case of chronic lymphocytic leukemia of the T cell type. Nuclear irregularities and CD3 positive immunostaining were typically present. In our experience, cytologic material was especially useful in identifying the peculiar nuclear shape of tumor cells in this category. There was no discrepancy between CB and excisional biopsy.

Miscellaneous (7 Cases)

Table 3 summarizes the results in this group. Correlation with excisional biopsy was possible in 3 cases (42.8%). CB diagnosis was incorrect in 1 NK cell lymphoma and in 1 T cell-rich B cell lymphoma.

DISCUSSION

In recent years, percutaneous image-guided CB has been used increasingly in the diagnosis of lymph node pathology as an alternative to surgi-

CORE BIOPSY OF MALIGNANT LYMPHOMAS

Case	Age/Sex	Location	CB Diagnosis	Excisional Diagnosis
1	23/F	lleon	Burkitt's lymphoma	ND
2	55/M	Spleen	NHL, B cell type	ND
3	78/M	Mesentery	NHL, B cell type	ND
4	54/M	Neck	NHL, high-grade	NHL, B cell type (autopsy)
5	56/F	Groin	Benign tissue, NOS	T-cell rich B cell lymphoma
6	48/M	Retroperitoneum	T cell–rich B cell lymphoma	ND
7	81/M	Axilla	Lymphoid proliferation	NK cell lymphoma

TABLE 3 Miscellaneous Group of 7 Miscellaneous Malignant Lymphomas Diagnosed on CB

Abbreviations: ND, not done; NHL, non-Hodgkin's lymphoma; NK, natural killer.

TABLE 4 Series of Image-Guided CB in Malignant Lymphoma

Study	Year	No. of Cases	Imaging Guidance	Overall Diagnostic Accuracy of CB
Kalkner et al⁵	1994	129	Ultrasound	87%
Ben-Yehuda et al ⁶	1996	100	СТ	78%
Pappa et al ⁷	1996	106	CT/Ultrasound	83%
Zinzani et al ¹⁵	1998	55	Ultrasound	87%
Zinzani et al ¹⁶	1999	83	CT/Ultrasound	81%
de Kerviler et al ¹⁷	2000	158	CT/Ultrasound	88%
Sklair-Levy et al ¹⁸	2000	49	СТ	71.5%
Demharter et al ¹⁹	2001	65	СТ	89.2%
Screaton et al ²⁰	2002	66	Ultrasound	80%
Agid et al ²¹	2003	267	СТ	82.5%
Goldschmidt et al ²²	2003	130	СТ	75.4%
Balestreri et al ²³	2005	137	СТ	87%
Sklair-Levy et al ²⁴	2005	114	CT/Ultrasound	84.2%
Li et al ²⁵	2005	80	СТ	76.2%
Ravinsky et al ²⁶	2005	28	СТ	82%
Present study	_	102	Ultrasound	88.2%

cal biopsy, particularly if the nodes are deepseated or if the clinical condition of the patient is severely impaired. Sonography and CT show similar success when in the hands of an experienced operator, but sonography is usually preferred because of its real-time capability.

The widespread use of this technique has detractors among pathologists, because the scarcity of the obtained material may make the diagnosis and/or subtyping of malignant lymphomas more difficult.⁴ Table 4 summarizes the accumulated experience in this domain and reflects that the diagnostic concordance between CB and surgical biopsy samples is high (71%-89%). These data support a more generalized use of this procedure. In fact, de Kerviler et al¹⁷ concluded in their study on 194 patients that the diagnostic approach of lymphoma should now be based on minimally invasive techniques, and Sklair-Levy et al,²⁴ after studying 114 cases of lymphoma using this method, state that image-guided coreneedle biopsy should be considered as a first-step method in the diagnosis of patients with superficial lymphadenopathies. Other authors²³ favor

its use in deep masses that would require general anesthesia for surgical removal, and still others^{7,25} advise it in the absence of palpable superficial lymph nodes.

Sonographic detection of superficial lymph nodes was first reported 2 decades $ago;^{27}$ since then, ultrasound-guided needle biopsy has shown good results in various sites, including the mediastinum,^{28,29} head and neck,³⁰ soft tissues,³ and spleen.³¹ CT has also been used to guide needle biopsies of the liver,³² spleen,³³ and pelvis and retroperitoneum.³⁴ Image-guided needle biopsy has also been successfully applied in pediatric patients.³⁵

In our experience, CB worked best in the LBCL group. Indeed, the identification of a dense population of large lymphoid cells with B cell immunophenotype in tissue cores is usually sufficient to confirm the diagnosis. We found somewhat similar results in the SBCL group, although small neoplastic lymphocytes may be mistaken for nonneoplastic elements if the tissue sample contains both populations. The presence of B cell lineage markers, together with the combined positivity for bcl-2 and bcl-6 in lymphoid cells, is diagnostic of follicular lymphoma. However, this combined immunostaining is not always unequivocal, particularly with bcl-2 and bcl-6 antibodies, which explains some incomplete diagnoses in our series. Small cells with CD5 and CD23 positivity, in addition to the clinical setting, are diagnostic of lymphocytic lymphoma/leukemia. As reported previously,^{23–25} HD is the most problematic diagnosis in CB in our series. The varied histologic approaches of this disease, the scarcity of the material for diagnosis, and the frequent absence of Reed-Sternberg cells in the submitted material are responsible for these difficulties. Though limited, our experience in the CB diagnosis of T cell lymphomas is satisfactory. Nuclear peculiarities of T cells and CD3-positive immunostaining are crucial in its recognition. We have not found any other reports on the diagnosis of T cell lymphoma in CB, but Yao et al,⁹ in their series of 33 cases, reported that fine needle aspiration cytology is

an accurate diagnostic method. The low frequency of T cell-rich B cell and NK cell lymphomas makes diagnosis very difficult and dependent on the quality of the submitted material. Finally, Burkitt's lymphoma diagnosis is favored by the typical clinical setting and histology.

Molecular analysis in our series was performed only to help the pathologic diagnosis and was particularly helpful in distinguishing follicular lymphoma from nonneoplastic lymphoid proliferations.

Ultrasound-guided needle biopsy is a useful method in the diagnosis of malignant lymphoma, but optimal results require experienced radiologists and pathologists. In fact, 9 out of 12 diagnostic failures occurred in the first 2 years of the study. Tight collaboration between clinicians, radiologists, and pathologists is the key to success. CB is especially useful in patients who are in poor clinical condition or in any situation that prevents an open surgical biopsy. Nonetheless, we believe that open lymph node biopsy still remains the standard procedure for the complete histopathologic diagnosis of some malignant lymphomas.

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