Value and Diagnostic Accuracy of Ultrasound-Guided Full Core Needle Biopsy in the Diagnosis of Lymphadenopathy

A Retrospective Evaluation of 793 Cases

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Objectives—Whole surgical lymph node excision (SNE) is considered the standard diagnostic method in the primary diagnosis of lymphadenopathy (LA) suspected of malignancy. Ultrasound-guided full core needle biopsy (UFCNB) offers an alternative method to SNE. This study examined the accuracy of UFCNB in the diagnosis of unexplained LA in 793 cases.

Methods—From January 2006 to June 2015, a total of 793 cases of LA of unknown origin received a UFCNB. The lymph nodes were located peripherally (68%) or abdominally (32%). The final diagnoses from histopathologic examinations were non-Hodgkin lymphoma (n = 245), Hodgkin lymphoma (n = 53), solid nonlymphocytic lymph node metastases (n = 359), and benign LA (n = 136). The results of the biopsies were retrospectively evaluated with regard to sensitivity, specificity, and diagnostic accuracy.

Results—In the total collective of 793 biopsies, the sensitivity of UFCNB was 94.4%; the specificity was 97.8%; and the diagnostic accuracy was 95.0%. In the subgroups, the following results were obtained: non-Hodgkin lymphoma (sensitivity, 97.2%), Hodgkin lymphoma (sensitivity, 88.7%), metastases (sensitivity, 93.3%), and benign LA (specificity, 97.8%). In 17 cases (2.2%), an additional rebiopsy of the lymph node was needed, and in 85 cases (10.7%), an additional SNE was performed.

Conclusions—Due to the diagnostic accuracy of 95.0% in the total collective, UFCNB seems to be an alternative diagnostic procedure to the standard procedure of SNE for LA of unknown origin. A prospective comparative study to definitively clarify the diagnostic value of UFCNB compared to SNE in the unexplained LA is warranted.

Key Words—lymphadenopathy; lymphoma; ultrasound-guided full core needle biopsy

A common problem in clinical practice is lymphadenopathy (LA) of unknown origin. The case history (history of a tumor and B symptoms), physical examination (consistency of LA, size, displacement in relation to the surrounding tissue, and pain from the LA), and B-mode ultrasound (US) imaging criteria (size and shape) can be helpful in the differentiation between malignant or benign LA.1,2 In cases of unexplained localized LA for
longer than 4 weeks, further diagnostic procedures are recommended. The standard diagnostic procedure in the diagnosis of a lymph node (LN) suspected of malignancy, especially malignant lymphoma, is the excision and histopathologic examination of the whole LN. Biopsy is already an established method in suspected LN metastasis. Nevertheless, minimally invasive techniques such as US-guided core needle biopsy (CNB) are increasingly used as diagnostic procedures in unknown LA suspected of malignant lymphoma. The complication rates of CNB (0%–8%) are lower than those of surgical lymph node excision (SNE; 1%–34%). In comparison to fine-needle biopsies (needle diameter <1 mm), good results in sensitivity, specificity, and diagnostic accuracy (98.1%, 100%, and 98.7%, respectively) were achieved in small case series using CNB (needle diameter >1 mm). In comparison to conventional CNB, the introduction of the new technology of ultrasound-guided full core needle biopsy (UFCNB) allows greater tissue gain in percutaneous biopsy and may be an alternative diagnostic procedure to SNE.

This study examined the diagnostic accuracy of UFCNB in the diagnosis of unexplained LA in 793 cases.

Materials and Methods

The Ethics Committee of the University Hospital in Marburg approved this study.

Patients

Over 9 years (January 2006–June 2015) a total 804 UFCNBs were performed in patients with peripheral or abdominal LA. Inclusion criteria for the retrospective analysis were the availability of complete documentation of the US examination, the performed biopsy, and the histopathologic examination results of the UFCNB specimen. Furthermore, the existence of a document with the final diagnosis (letter of discharge) was required. Due to incomplete documentation of the data, 11 cases were excluded (4 cases with no letter of discharge, 3 cases with no definitive diagnosis, and 4 cases with incomplete data documentation).

Finally, 793 cases were included in the study. The histologic specimen from the UFCNB was subsequently examined in the local pathology department. In 239 cases (30%), the specimen was additionally sent to a reference center. A reference pathologic report was obtained at the discretion of the local pathologist or treating physician in cases of uncertainty about the correct diagnosis, especially in patients with lymphoma for subtype differentiation. An UFCNB was performed by an examiner (C.G.) with greater than 35 years of US experience.

The following data were retrospectively extracted from the medical records: clinical data (age and sex), indication for UFCNB (primary diagnosis or recurrence diagnosis), US data such as the LN location (peripheral or abdominal) and size (length and width) of the punctured LN, existence of a histopathologic reference review (yes or no), execution of rebiopsy (yes or no), execution of an additional SNE of the biopsied LN (yes of no), final clinical diagnosis (clinical discharge letter), and performance of clinical or US follow-up of benign LA (yes or no).

Procedure

All patients with persistent LA were examined with B-mode US. The size, echo morphologic characteristics, and shape were documented. Suspected LA was classified by the Solbiati index (width-to-length ratio <2), echogenicity (hypoechoic), structural inhomogeneity, a missing hilar sign and disturbed architecture on B-mode US imaging, and color Doppler appearance for vascular patterns. The patient’s medical history and clinical data (history of malignant disease, B symptoms, and other tumor manifestations), as well as the US evaluation of the LN were assessed by an experienced examiner (C.G.). The decision to perform UFCNB was based on US LN characteristics that were suspicious for malignancy. Basically, UFCNB was executed with an 18-gauge needle after exclusion of contraindications (platelets <50 G/L, quick value <50%, and anticoagulant or double-platelet inhibition therapy) and with written consent by the patient. All examinations were performed with Acuson Sequoia 512 US machines (Siemens AG, Erlangen, Germany) equipped with linear or curved array transducers.

The UFCNB was performed in real time under sterile conditions with local anesthesia (10 mL of 1% Ultracain; Sanofi, Paris, France). The most suspect LN was detected with B-mode US; additionally, color Doppler US was used to visualize LN vascularization to avoid any large-vessel injury and biopsy of necrotic areas of the LN. The depth of the LN was assessed to better adjust the biopsy instrument to the size of the suspicious LN. The depth of the LN was measured because the advancement of the biopsy instrument
depended on the LN size. The throw length had to be determined on the biopsy instrument before the biopsy. It varies between 13 mm (yields a 9-mm specimen length), 23 mm (yields a 19-mm specimen length), and 33 mm (yields a 29-mm specimen length). Targeted biopsy was executed in real time with position control using a needle guide device that was fixed to the US transducer. Every specimen was conserved in an adequately labeled tube containing 1% formaldehyde. The duration of the whole procedure was about 10 to 15 minutes. After the procedure, the biopsy site was compressed by a small sandbag for 2 hours to avoid bleeding complications, and the patient’s condition was monitored. In cases of complaints or an ambulatory intervention, a control B-mode US examination was performed 2 hours after the intervention. Figure 1 presents an abdominal lymphoma bulk (Figure 1A), followed by a US-guided biopsy of the bulk (Figure 1B).

Figure 1. A. Hypoechoic presentation of abdominal lymphoma on B-mode imaging with the presentation of a large vessel on power Doppler imaging. B. Ultrasound-guided core needle biopsy of the abdominal lymphoma mass.
Statistical Analysis
For calculation of the sensitivity and specificity of UFCNB, a conservative approach was used, which means that the number of nodes with inadequate biopsies were added to the denominator. Ninety-five percent confidence intervals (CIs) were determined by the exact method of Clopper and Pearson.25 Likelihood ratios were calculated from the obtained sensitivities and specificities, and the 95% CIs were based on the method of Simel et al.26

For all calculations, correct positive was defined as a correct malignant pathologic diagnosis of a malignant LN and correct negative as a correct benign pathologic diagnosis of a benign LN. To validate whether the diagnostic accuracy differed in subgroups, a $\chi^2$ test was applied.

Results

Clinical Data
The study collective consisted of 793 biopsy samples from 735 patients: 430 (59%) male and 305 (41%) female. Their mean age was 60 years, ranging from 11 to 90 years. Over the 9 years, 691 patients had 1 biopsy; 31 patients were punctured twice; 12 patients had 3 biopsies; and 1 patient was punctured 4 times, resulting in a total of 793 punctures, henceforth referred to as cases (Table 1). Despite the fact that some patients were punctured multiple times over the 9-year recruiting period because of a new LA, all-single puncture results were evaluated as independent cases. From the 793 biopsies, 329 (41.5%) were performed as part of the primary diagnosis (no history of a malignant disease), and 464 (58.5%) were performed in the course of a suspected relapse, a progressive disease, or a suspected secondary malignancy.

Ultrasound Data
A total of 537 peripheral biopsies (68%) and 256 abdominal biopsies (32%) were performed. The most frequent locations in the peripheral biopsies were cervical (187 [35%]), followed by supraclavicular (100 [19%]), inguinal (89 [17%]), and axillary (77 [14%]). The most frequent abdominal biopsy sites were mesenteric (90 [35%]), para-aortic (73 [29%]), and iliacal (57 [22%]).

The sizes of the biopsied LNs could be retrospectively analyzed in only 608 cases (77%) of the procedures; in 185 cases (23%), the sizes of the LNs were not documented. The most frequent diameter was between 1.1 and 2.0 cm (206 [34%]), followed by a diameter of greater than 2.1 cm (118 [19%]). Ninety-four (15%) of the biopsied LNs had a diameter of less than 1.0 cm. The smallest diameter of a punctured LN was 0.3 cm, and the largest LN had a diameter of 20 cm.

Diagnostic Results in General
In the 793 UFCNB study cases, the final diagnoses from the physicians’ discharge letters were as follows: 359 (45.3%) metastases of solid tumors, 298 (37.6%) LN involvement of malignant lymphomas, and 136 (17.1%) benign causes of LA (Table 2).

Table 1. Overview of Patients and Total Biopsies

| Characteristic       | n   | %  |
|----------------------|-----|----|
| Patients             | 735 | 100|
| Female               | 305 | 41 |
| Mean age ± SD, y     | 69.4 ± 171 | 79 |
| Male                 | 430 | 59 |
| Mean age ± SD, y     | 59.8 ± 15.4 | 79 |
| Total biopsies       | 793 | 100|
| 1 biopsy per patient | 691 | 87.1|
| 2 biopsies per patient | 31  | 78 |
| 3 biopsies per patient | 12  | 4.6|
| 4 biopsies per patient | 1   | 0.5|

Table 2. Overview of the Final Diagnoses With Main Groups and Subgroups

| Final Diagnosis                        | n   | %  |
|----------------------------------------|-----|----|
| Total cases                            | 793 | 100|
| Solid tumors                           | 359 | 45.3|
| Carcinoma                              | 291 | 81.0|
| Sarcoma                                | 6   | 1.7 |
| Malignant melanoma                     | 24  | 6.7 |
| Germ cell tumor                        | 19  | 5.3 |
| Cancer of unknown primary site          | 16  | 4.5 |
| Chloroma                               | 3   | 0.8 |
| Lymphoma                               | 298 | 37.6|
| HL                                     | 53  | 17.8|
| NHL                                    | 245 |     |
| Indolent NHL                           | 116 | 38.9|
| Aggressive NHL                         | 127 | 42.6|
| Other                                  | 2   | 0.7 |
| Benign diseases                        | 136 | 17.1|
| Unknown origin                         | 85  | 62.5|
| Infectious                             | 22  | 16.2|
| Immunologic                            | 17  | 12.5|
| Benign neoplasia                       | 12  | 8.8 |
**Subclassifications**

The subclassification of the 359 (45.3%) cases with solid tumors revealed a wide spread of different diagnoses, whereas 41 cases of non–small cell lung cancer constituted the most common entity (11.4% of solid tumors). Among the 298 cases (37.6% of overall cases) with malignant lymphomas, the subclassification revealed 245 (82.2%) non-Hodgkin lymphomas (NHLs; 220 B-cell lymphomas, 23 T-cell lymphomas, and 2 post-transplantation lymphomas). Hodgkin lymphoma (HL) was diagnosed in 53 (17.8%) cases.

Benign LA was found in 136 (17.2%) cases and included LA of reactive/unknown causes (85 [62.5%]), infectious causes (22 [16.2%]), immunologic disorders (17 [12.5%]), and other benign diseases (12 [8.8%]) including schwannoma (3), leiomyoma (2), ganglion enlargement (1), histiocytoma (1), lymphangiectasis (1), Castleman disease (1), oncocytoma of the submandibular gland (1), paraganglioma (1), and type A thymoma (1).

**Additional Procedures**

Generally, additional procedures were ordered by the clinician. In 239 cases (30.1%), a secondary additional examination of the specimen was performed by a reference pathologist. In all of these cases, the final diagnosis (letter of discharge) was made according to diagnosis of the reference pathologist. In 88 of 239 cases (36.8%) after the reference assessments.

In 17 cases (2.2%), an additional UFCNB was performed for different causes: inadequate material in the first biopsy (n = 4), negative biopsy result in a suspected clinical malignant LN (n = 6; 4 of 6 LNs were malignant after rebiopsy, and 2 of 6 were still benign), further verification of a malignant LN (n = 6), and 1 for a renewed diagnosis in a case of sample confusion.

In another 85 cases (10.7%), an additional SNE was performed after UFCNB. These included 63 of 85 cases (74.1%) for further diagnostic reasons caused by persistent LA. In these cases, the histopathologic specimens from the UFCNB were not sufficient or uncertain for a proper diagnosis (22 carcinomas, 22 benign diseases, and 19 lymphomas). In 17 cases (20.0%), SNE was performed as part of therapeutic procedures (15 metastases, 1 lymphoma, and 1 benign disease). In 5 cases (5.9%), the SNE was executed because of inadequate UFCNB material (2 lymphomas, 2 benign diseases, 1 metastasis). However, in 18 of the 85 cases (21.2%), there was a difference.

**Table 3. Results of the Histologic Diagnoses From UFCNB in Comparison With the Diagnoses From SNE in 85 Cases**

| Diagnosis From UFCNB | Diagnosis From SNE |
|---------------------|--------------------|
| Adenocarcinoma (n = 11) | Adenocarcinoma of the colon (n = 5) |
| Non–small cell lung cancer (n = 1) | Small cell lung cancer (n = 1) |
| Carcinoma of the ampulla of Vater (n = 1) | Adenocarcinoma of the rectum (n = 1) |
| Papillary carcinoma of the thyroid (n = 2) | |
| Peritoneal carcinoma (n = 1) | Peritoneal carcinoma (n = 1) |
| Merkel cell carcinoma (n = 1) | Merkel cell carcinoma (n = 1) |
| Malignant melanoma (n = 15) | Malignant melanoma (n = 15) |
| Neuroendocrine tumor (n = 2) | Epithelial carcinoma (n = 1) |
| Pulmonary neuroendocrine tumor (n = 1) | Plate epithelial carcinoma (n = 2) |
| Plate epithelial carcinoma (n = 2) | Gastrointestinal stromal tumor (n = 1) |
| Spindle cell tumor (n = 2) | Spindle cell sarcoma (n = 1) |
| NHL (n = 11) | NHL (n = 10) |
| Necrotic tissue (n = 1) | HL (n = 4) |
| Histiocytoma (n = 1) | Histiocytoma (n = 1) |
| Thymoma (n = 1) | Thymoma (n = 1) |
| Reactive LA (n = 15) | Castleman disease (n = 1) |
| Reactive LA (n = 22) | Reactive LA (n = 1) |
| Granulomatous inflammation (n = 2) | Echinococcus multilocularis infection (n = 1) |
| Fibrotic inflammation (n = 1) | Fibrotic inflammation (n = 1) |
| Fibrine necrosis (n = 1) | Sarcoma (n = 1) |
| Leiomyomatous neoplasm (n = 1) | Leiomyoma (n = 1) |
| Sclerotic LN tissue (n = 2) | HL (n = 1) |
| Inadequate material (n = 4) | Sclerotic LN tissue (n = 1) |
| Tissue necrosis (n = 1) | NHL (n = 2) |

Wilczynski et al—Ultrasound-Guided Full Core Needle Biopsy of Lymphadenopathy
between the histopathologic results from the UFCNB and the SNE (7 NHLs, 3 HLs, 5 metastases, and 3 benign diseases). Detailed data are presented in Table 3. The final diagnosis (letter of discharge) in the discrepant results was based on the standard procedure of SNE.

Follow-up
In the group of 136 benign LNs, diagnoses were confirmed in 100 cases (73.5%) by clinical/US follow-up without evidence of a malignant disease. In 36 cases (26.5%), no follow-up was documented. In 72 of the 85 cases of reactive/unknown LA, a follow-up was documented: clinical follow up (32 of 72), US follow-up (31 of 72), and additional SNE in the remaining cases (9 of 72).

Complications
In 11 cases (1.4%), biopsy-associated complications were documented. In 6 cases, minor bleeding was observed, which could be stopped by wound compression and required no further therapies/interventions. In 4 cases, there was a hematoma in the location of the puncture, and in one case, a major complication occurred with active bleeding after biopsy of a cervical LN. In this case, surgery was needed. The histopathologic examination of the LN revealed a venous malformation within a cervical LN.

Diagnostic Accuracy
In the total collective of 793 biopsies, the number of adequate biopsy samples obtained by UFCNB was 782 (98.6%). Of the 793 there were 11 (1.4%) histologic samples from UFCNB that were initially inadequate for histologic examinations (5 with no lymphatic tissue, 3 with necrotic tissue, 2 with no vital tissue, and 1 for which no diagnosis on the biopsy sample was possible).

A total of 753 cases were correctly diagnosed; 620 of these were correct positive, and 133 were correct negative (Table 4). In 29 cases, the histologic results from the UFCNB were false-negative. None of the cases showed false-positive results. The sensitivity of the biopsy in the total collective was 94.4% (95% CI, 92.3%–96.0%); the specificity was 97.8% (95% CI, 93.7%–99.5%), and the diagnostic accuracy was 95.0% (95% CI, 93.2%–96.4%). The positive likelihood ratio of the UFCNB was 42.78 (95% CI, 13.97–131.01). The likelihood ratio confirmed the value of the diagnostic tests.

In the group of 359 cases with metastases of solid-tumor diseases, 335 cases were rated as correct positive. In 20 cases, the biopsy revealed a false-negative result. The sensitivity was 93.3% (95% CI, 90.2%–95.7%). The results of UFCNB in the group of malignant lymphomas were correct positive in 285 cases, and in 9 cases the results of the puncture were false negative. The sensitivity in the group of lymphomas was 95.6% (95% CI, 92.6%–97.7%).

Among the subgroup of NHLs, the test results were correct positive in 238 cases with a total of 245 biopsies. The test results were false negative in 3 cases. The sensitivity in the group of NHLs was 97.2% (95% CI, 96.4%–99.7%). Among the HLs (53), the number of correctly diagnosed cases was 47, and 6 cases had false-negative results. The sensitivity in the HL subgroup was 88.7% (95% CI, 77.0%–95.7%).

| Table 4. Presentation of test results in the total collective of 793 cases and of the results of both diagnostic procedures (UFCNB and SNE) in 85 cases |
|----------------------------------|------------------|------------------|------------------|
| **Result**                       | **Final Diagnosis** | **Sensitivity/Specificity, %** | **Positive/Negative Likelihood Ratio** |
|                                 | Malignant | Benign |                                 |                                     |                                     |
| Biopsy                          | 657       | 136    | 94.4 (92.3–96.0)                 | 42.78 (13.97–131.01)                |
| Malignant                       | 620       | 0      | 97.8 (93.7–99.5)                 | 0.06 (0.04–0.08)                    |
| Benign                          | 29        | 133    |                                 |                                     |
| Inadequate                      | 8         | 3      |                                 |                                     |
| Compared with SNE               | 57        | 28     | 84.2 (72.1–92.5)                 | 4.72 (2.11–10.52)                   |
| Positive                        | 48        | 0      |                                 |                                     |
| Negative                        | 8         | 23     | 82.1 (63.1–93.9)                 | 0.19 (0.10–0.36)                    |
| Inadequate                      | 1         | 5      |                                 |                                     |

Values in parentheses are 95% CIs.
In 85 cases (10.7%), a direct comparison between the histological diagnosis from UFCNB and SNE was possible because both procedures were performed (Table 4). The sensitivity was 84.2% (95% CI, 72.1%–92.5%); the specificity was 82.1% (95% CI, 63.1%–93.9%); the diagnostic accuracy was 83.5% (95% CI, 73.9%–90.7%); and the positive likelihood ratio was 4.72 (95% CI, 2.11–10.52).

There was no statistically significant difference regarding the diagnostic accuracy between peripheral and abdominal LN biopsies (P = .507) and primary diagnosis or diagnosis in relapsed disease (P = .599). Moreover, no statistically significant difference was found in the accuracy between a size of LNs of less than 1.0 cm in diameter or 1.0 cm or greater in diameter (P = .603).

Discussion

The diagnostic workup of suspected malignant LA critically depends on obtaining sufficient and representative tissue specimens. Surgical node excision remains the standard diagnostic procedure for obtaining tissue in cases of suspected malignant lymphoma.27 Only in cases without easily accessible LNs does the European Society for Medical Oncology recommend minimally invasive biopsy techniques as alternative diagnostic procedures.27,28 In daily clinical practice, however, minimally invasive biopsy techniques, such as fine-needle biopsy (inner needle diameter < 1 mm) and CNB (inner needle diameter > 1 mm), have largely replaced SNE. This is because CNB and fine-needle biopsy methods are fast and effective diagnostic procedures that can be safely performed by experienced physicians even in an outpatient setting. Although the fine-needle biopsy material is often too small for a complete immunohistochemical analysis in cases of suspected malignant lymphoma, CNB overcomes this disadvantage by producing larger tissue samples.32 Core needle biopsy is also considerably less expensive than SNE.32 Ultrasound-guided full core needle biopsy, as used in this study, is a variant method of CNB, which allows even more (from 30% to 59%) tissue recovery than conventional CNB.20,33 Indeed, in this study, UFCNB resulted in adequate material recovery in 98.6% of cases. Although an additional diagnostic procedure (rebiopsy or SNE) was performed in 12.9%, the diagnostic accuracy of UFCNB was 95.0% for the entire cohort and thus well comparable to CNB.8,12,19,32,34,35 A high diagnostic accuracy rate of 95.6% was also seen in the subgroup of patients with lymphoma involvement, for which diagnostic accuracy rates of 90% and 99.3% were reported, respectively, in 2 previous studies using CNB.19,36 Discrepant histopathologic results between UFCNB and SNE were observed in 18 of the 85 selected patients, in whom an additional SNE was performed. Reasons for performing a secondary histologic examination after UFCNB varied, but included insufficient sampling, uncertainty about pathologic results raised by the treating physician, and a sampling error. However, if one assumes that the diagnosis was correctly obtained in all cases that did not receive a second intervention (691), or the diagnosis was confirmed by the second intervention (75), UFCNB provided a correct diagnosis in 766 of 793 specimens (96.6%) in this study, which was remarkably good. A smaller previous study compared 14-gauge CNB with SNE and found discrepant diagnostic results in 9.1% of cases.37 In another study, CNB and SNE were prospectively compared, and superiority was seen for CNB.18 Thus, a comparison of the diagnostic accuracy of SNE versus CNB or FCNB is warranted. However, for a head-to-head comparison of the diagnostic accuracy of both methods, sampling should be prospectively performed in the same patient and by applying both UFCNB and SNE sequentially on the same suspicious LN.

Another important factor favoring CNB/UFCNB is the consistently lower rate of postinterventional complications compared to SNE (0% to 8% versus 1% to 34%11–18). In our UFCNB cohort, only 11 cases had complications (1.4%). Only 1 patient had a major complication requiring surgical intervention.

Limitations of this study were its retrospective design and the fact that data reflected only a single-center experience. This is an important issue regarding the generalizability of our results. For example, it is well established that interobserver variability and US experience have a major impact on results.18 In this study, all LN biopsies were performed by an examiner with greater than 35 years of US experience. Together, the results from this very large cohort of patients demonstrate that - in the hands of an experienced examiner - UFCNB has a remarkably high diagnostic specificity (97.8%), sensitivity
(94.4%), and accuracy (95.0%) for the histopathological workup of enlarged LNs suspicious for malignancy. Moreover, UFCNB proved to be a convenient procedure for physicians and patients, with a low rate of postinterventional complications. We conclude that in the absence of controlled data, our results strongly support the current clinical practice of performing UFCNB as the primary diagnostic procedure for unclear LA.

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