Formulating a treatment plan in suspected lymphoma: Ultrasound-guided core needle biopsy versus core needle biopsy and fine-needle aspiration of peripheral lymph nodes

Monica R. Drylewicz  
*Washington University School of Medicine in St. Louis*

Marcus P. Watkins  
*Washington University School of Medicine in St. Louis*

Anup S. Shetty  
*Washington University School of Medicine in St. Louis*

Michael F. Lin  
*Washington University School of Medicine in St. Louis*

Amber Salter  
*Washington University School of Medicine in St. Louis*

*See next page for additional authors*

Follow this and additional works at: [https://digitalcommons.wustl.edu/open_access_pubs](https://digitalcommons.wustl.edu/open_access_pubs)

Recommended Citation

[https://digitalcommons.wustl.edu/open_access_pubs/7863](https://digitalcommons.wustl.edu/open_access_pubs/7863)

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.
EcoVue® Ultrasound Gel

Change Your Vue.
Ergonomically designed for ease-of-use, the eco-friendly FlexPac® creates higher product-to-package ratio reducing waste and improving sustainability. Designed with patient safety in mind, our non-refillable & single use products will forever Change Your Vue of ultrasound gel.

Introducing the next generation of Ultrasound Gel

- Sustainable Packaging
- Natural Ingredients
- Reduces CO² Footprint

20g Packet
Sterile & Non-Sterile

32g FlexPac®
Sterile & Non-Sterile

60g Flip-Top Tube
Non-Sterile

250g FlexPac®
Non-Sterile

EcoVue.com
Formulating a Treatment Plan in Suspected Lymphoma

Ultrasound-Guided Core Needle Biopsy Versus Core Needle Biopsy and Fine-Needle Aspiration of Peripheral Lymph Nodes

Monica R. Drylewicz, MD, PhD, Marcus P. Watkins, PhD, Anup S. Shetty, MD, Michael F. Lin, MD, Amber Salter, PhD, Nancy L. Bartlett, MD, William D. Middleton, MD, Motoyo Yano, MD, PhD

Objectives—Image-guided tissue sampling in the workup of suspected lymphoma can be performed by core needle biopsy (CNB) or CNB with fine-needle aspiration (FNA). We compared the yield of clinically actionable diagnoses between these methods of tissue sampling.

Methods—All ultrasound-guided percutaneous peripheral lymph node biopsies from 2010 to 2017 at a single institution were retrospectively reviewed for biopsy type (CNB versus CNB + FNA), prior diagnosis of lymphoma, size of the target lymph node, number of cores, length of core specimens, and pathologic diagnosis. Lymphoma and lymphoid tissue were included; metastatic disease and nonlymphoid tissue were excluded. An oncologist specializing in lymphoma independently determined whether an actionable diagnosis could be made with the pathologic results in the context of the patient’s medical record. χ² analyses and univariable/multivariable logistic regression models were used for statistical analyses.

Results—Of 578 lymph node biopsies, 306 (53%) had a prior diagnosis of lymphoma; 273 (47%) were CNB, and 305 (53%) were CNB + FNA. There was no significant difference between biopsy types (CNB versus CNB + FNA) in the number of cores (median [25th, 75th percentiles], 3 [3, 4] versus 4 [3, 4]; P = .47) or total length of tissue (4.1 [2.5, 6.1] versus 3.7 [2.3, 6] cm; P = .09). There was no difference in obtaining an actionable diagnosis between biopsy types after controlling for a known history of lymphoma (P = .271) or after controlling for the number of core specimens (P = .826).

Conclusions—In cases of suspected lymphoma, CNB without FNA was sufficient to obtain an actionable diagnosis.

Key Words—biopsy; core; fine-needle aspiration; lymphoma; ultrasound guided

Lymphoma is a broad category of diseases encompassing malignancies of the lymphocyte (B cells and T cells). There are more than 50 different subtypes of lymphoma in the most recent classification system,¹ the treatment and prognosis of which vary considerably. Patients may present with vague symptoms such as low-grade fever and weight loss, palpable lymphadenopathy, or altered hematologic laboratory values. The diagnostic evaluation for lymphoma requires tissue for determination of the presence of lymphoma and disease subclassification to formulate a treatment plan.¹

Multiple methods may be used to obtain tissue for histopathologic analysis, including excisional/incisional biopsy and image-guided
percutaneous tissue sampling by core needle biopsy (CNB) or fine-needle aspiration (FNA). Although there is no clear recommendation by the American Cancer Society as of 2016, the European Society of Medical Oncology recommends surgical excision whenever possible. However, in our experience, many physicians, including those with expertise in lymphoma, prefer percutaneous biopsy given its less-invasive nature, ease of scheduling, lower cost, and generally high yield of diagnostic data. Core needle biopsy uses a spring-loaded side notch or hollow-bore needle to obtain a solid core of tissue from the target lesion. Fine-needle aspiration uses multiple small-gauge needles with rapid back-and-forth motion in the target lesion to collect individual cells in the needle tip. Core biopsies, when intact, retain some architectural context, whereas FNA loses all such tissue information, relying solely on individual cellular characteristics for diagnosis.

There is a large volume of literature investigating the diagnostic yield of tissue sampling in the setting of suspected lymphoma. Many of these studies have addressed whether image-guided biopsy performs adequately compared to excisional biopsy in the diagnosis and treatment of lymphoma. Fine-needle aspiration alone is clearly inadequate compared to excisional biopsy. The success rate of CNB alone in yielding a clinically actionable diagnosis ranges from 67% to 100%. Some of the highest yields considered only patients with a history of lymphoma (90%–97%) or reported the success rate of subclassification when lymphoma was diagnosed on the biopsy (100%). In our practice, CNB and FNA of the same target lesion are often requested and performed to collect tissue for histopathologic analysis and flow cytometry. However, performing both CNB and FNA increases the procedural time as well as cost and, potentially, patient anxiety. We performed this study given the paucity of data comparing the actionable yield of CNB compared to CNB + FNA.

**Materials and Methods**

A cohort of patients with lymphadenopathy biopsied with ultrasound guidance at our institution between July 1, 2010 and December 31, 2016, was retrospectively reviewed. The patient cohort was obtained by a Health Insurance Portability and Accountability Act-compliant, Institutional Review Board–approved search of our institutional radiology database, Montage (Nuance Communications, Burlington, MA). Informed consent was waived by the Institutional Review Board. Biopsy of superficial lymphadenopathy was performed by searching for studies given a Current Procedural Terminology code for needle biopsy of lymph nodes (code 38505) exclusive of breast. Excluding the term “breast” was done to eliminate the large number of axillary lymph node biopsies performed to diagnose metastatic breast cancer. For patients with multiple biopsies, whether it be on the same or different dates, only the first biopsy performed was included for analysis. Therefore, each biopsy corresponded to an individual patient. Biopsies performed for research, those without a final pathology report, those coded incorrectly, and those yielding a diagnosis of metastasis, another mass, or no lymphoid tissue were excluded.

Several data points were collected for each biopsy and are detailed in Table 1. These data points included patient sex, age, date of biopsy, whether the patient had a prior diagnosis of lymphoma, location of the biopsy, largest dimension of the target lesion, type of biopsy performed (CNB or CNB + FNA), CNB gauge, and number of CNB passes. Core needle biopsy specimens were placed in formalin and submitted to surgical pathology for interpretation. Fine-needle aspiration specimens were submitted in RPMI solution for flow cytometry with the assistance of our sonographers. No pathologist was present at the time of CNB or FNA. Reported complications of the procedure were recorded. Minimum and maximum lengths of the core samples received by pathology and the pathologic diagnosis were recorded. The total length of CNB tissue was estimated as follows: [(number of cores – 1) × maximum core length recorded by pathology] + minimum core length recorded by pathology.

The hematology/oncology team specializing in lymphoma then independently reviewed the pathologic diagnosis as well as other available data from the patient’s medical record. A binary decision was rendered, determining whether the diagnosis was actionable. A diagnosis was considered actionable if the pathologic diagnosis considered within the context of the patient allowed either for initiation of treatment or final determination of benignity requiring no further intervention.
Table 1. Patient and Biopsy Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>CNB</th>
<th>CNB + FNA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>273</td>
<td>305</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>62 [49, 70]</td>
<td>54 [39, 65]</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>.212</td>
</tr>
<tr>
<td>Male</td>
<td>160 (58.6)</td>
<td>163 (53.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>113 (41.1)</td>
<td>142 (46.6)</td>
<td></td>
</tr>
<tr>
<td>Prior lymphoma diagnosis, n (%)</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>63 (23.1)</td>
<td>208 (68.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>210 (76.9)</td>
<td>97 (31.8)</td>
<td></td>
</tr>
<tr>
<td>Biopsy location, n (%)</td>
<td></td>
<td></td>
<td>.0008</td>
</tr>
<tr>
<td>Cervical/</td>
<td>95 (34.8)</td>
<td>150 (49.2)</td>
<td></td>
</tr>
<tr>
<td>supraclavicular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td>86 (31.5)</td>
<td>82 (26.9)</td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>84 (30.8)</td>
<td>67 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.9)</td>
<td>6 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Maximum target size, cm</td>
<td>3.3 [2.2, 4.1]</td>
<td>3.2 [2.1, 4.0]</td>
<td>.5</td>
</tr>
<tr>
<td>CNB gauge, n (%)</td>
<td></td>
<td></td>
<td>.889</td>
</tr>
<tr>
<td>16</td>
<td>19 (6.9)</td>
<td>21 (6.8)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>253 (92.7)</td>
<td>282 (92.4)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1 (0.4)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Cores, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>67 (24.5)</td>
<td>61 (20.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>79 (28.9)</td>
<td>88 (28.8)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60 (22.0)</td>
<td>111 (36.4)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>67 (24.5)</td>
<td>45 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Cores, n</td>
<td>3 [3, 4]</td>
<td>4 [3, 4]</td>
<td>.47</td>
</tr>
<tr>
<td>Estimated length, cm</td>
<td>4.1 [2.5, 6.1]</td>
<td>3.7 [2.3, 6.0]</td>
<td>.09</td>
</tr>
</tbody>
</table>

Data are presented as median [25th, 75th percentiles] (range) where applicable. Statistical significance was determined by the Wilcoxon rank sum test for continuous variables and the χ² test for categorical variables.

Descriptive statistics were used to summarize patient and biopsy characteristics using medians [25th, 75th percentiles] for continuous variables and frequency (percent) for categorical variables. Differences in characteristics and actionable diagnoses between CNB and CNB + FNA were compared by Wilcoxon rank sum or χ² square tests as appropriate. A Cochran-Mantel-Haenszel test was used to evaluate the association of an actionable diagnosis and biopsy controlling for a history of lymphoma. The association between the number of cores and target size was evaluated by a Spearman correlation. Multivariable logistic regression models were used to evaluate the association of the number of cores and CNB gauge with an actionable diagnosis. Statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc, Cary, NC).

Results

The initial search yielded 908 superficial lymph node biopsies performed with ultrasound guidance. A total of 25 biopsies were performed for research; 13 were incorrectly coded; and 12 were missing pathologic results. A total of 858 biopsies were analyzed: 259 yielded metastatic disease; 6 yielded a diagnosis of another mass (1 Warthin tumor, 3 peripheral nerve sheath tumors, 1 myoepithelial cyst, and 1 lymphoepithelial cyst); and 15 showed no lymphoid tissue (generally showing necrosis or muscle on pathologic specimens). These were excluded from the analysis. A total of 578 biopsies yielded a diagnosis of lymphoma or benign/indeterminate lymphoid tissue and were further analyzed by our oncology team.

Of the 578 biopsies used for analysis, 273 were CNB, and 305 were CNB + FNA (Table 1). These patient populations were similar in sex distribution (58.6% versus 53.4% male, respectively). Patients undergoing CNB alone were significantly older than patients undergoing CNB + FNA (62 [49, 70] versus 54 [39, 65] years, respectively; P < .01). When comparing the proportion of patients with a history of lymphoma between the biopsy types, more patients undergoing CNB alone had a prior diagnosis of lymphoma (76.9% versus 71.5%; Table 2). However, after controlling for a history of lymphoma, there was no significant difference in obtaining an actionable diagnosis between CNB versus CNB + FNA (P = .271; Table 3). There was no significant association between achievement of an
actionable diagnosis and the number of cores 
\((P = .826)\) or needle gauge \((P = .172, 18 \text{ versus } 16 \text{ gauge}; \text{ and } P = .088, 18 \text{ versus } 20 \text{ gauge}).

Of the 578 biopsies, only 3 minor complications were documented: 2 small hematomas \((18\text{-gauge CNB})\) and 1 case of left-hand numbness \((18\text{-gauge CNB }+ \text{ FNA})\), which resolved, presumed related to lidocaine infiltration of the axillary nerve. These findings correspond to a minor complication rate of 0.5%, with no major complications.

Discussion

The data from this retrospective study demonstrate that CNB alone performs as well as CNB + FNA in achieving an actionable diagnosis, after controlling for a history of lymphoma. Our study reflects clinical workflow, as the oncologist made the determination of whether an actionable diagnosis was achieved through biopsy and pathologic diagnosis, and differs from other diagnostic yield investigations, which use lymphoma subclassification as the end point. This approach is likely more clinically relevant, as the pathologic diagnosis is interpreted within the context of an individual patient. For example, there may be high clinical suspicion for transformation of a previously subclassified lymphoma, which is not reflected in the pathologic specimen because of a sampling error. In our study, this discrepancy would be classified as not achieving an actionable diagnosis, whereas if subclassification were the end point, it would be categorized as a successful case. Because of these differences in study methods, our results are not directly comparable to other studies.

Our study demonstrated a greater yield of actionable diagnoses in patients with a history of lymphoma \((82.4\%–88.1\%)\) as opposed to those without a known history \((66.4\%–68.2\%)\), consistent with the literature.\(^7,10,13\)

In our comparison of CNB to CNB + FNA, we found that the mean age of patients undergoing CNB

**Figure 2.** Number of cores obtained by target size. Boxes represent the 25th and 75th percentiles, with vertical lines within the boxes representing the medians, and lines extending from the boxes indicating the minimum and maximum values. The graph shows the distribution of the number of cores obtained by either CNB or CNB + FNA based on the size of the targeted lymph node. There is no correlation between the number of cores of obtained and the size of the targeted lymph node \((r = 0.08)\).

**Table 2.** Actionable Diagnosis by Biopsy Type

<table>
<thead>
<tr>
<th>Actionable Diagnosis</th>
<th>CNB</th>
<th>CNB + FNA</th>
<th>Total</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, n (%)</td>
<td>45</td>
<td>87</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>228</td>
<td>218</td>
<td>446</td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>273</td>
<td>305</td>
<td>578</td>
<td>.0006</td>
</tr>
</tbody>
</table>

Statistical significance was determined by the \(\chi^2\) test.
alone was older than that of those undergoing CNB + FNA. We also found that patients with a history of lymphoma were more likely to undergo CNB alone rather than CNB + FNA. These findings are consistent with our institutional practice of performing CNB + FNA rather than CNB alone for new potential diagnoses of lymphoma in which patients are often younger than those with established diagnoses who have recurrent disease after treatment.

We found that the number of core specimens obtained did not affect the actionable yield. This finding seems counterintuitive given the general propensity of pathologists to desire more tissue. Given the retrospective nature of this study, it is difficult to determine with certainty the reason why more tissue did not result in a greater yield. The pathology and radiology reports did not specify the total length of tissue obtained, and it is possible that our core length estimations were incorrect, especially if the core specimens were highly fragmented, a data point that was not available in the radiology report. However, the number of cores submitted also did not affect the actionable yield. As the number of cores obtained was at the discretion of the performing radiologist, it is possible that more core specimens were thought to be of low quality. It is also possible that pathologist satisfaction with fewer cores or the method used by pathology in the review of specimens negated the impact of a greater number of cores.

Although the large population size is a major strength of our study, there were several limitations. First, because of its retrospective design, data points pertaining to the length and quality of cores were inaccessible. Second, this study was limited to peripheral lymph nodes and may not necessarily apply to deeper locations such as retroperitoneal lymph nodes, sampled under computed tomographic guidance. Third, the calculated yield of actionable diagnoses did not include failed procedures meant to sample lymphoid tissue, and inclusion of these cases may have decreased our overall yield but would apply to both methods of tissue sampling. In fact, no case was found in which FNA obtained an actionable diagnosis when the CNB showed no lymphoid tissue.

In patients with a suspected new diagnosis of lymphoma, current practice at our institution is to perform CNB and FNA concurrently, whereas in cases with a history of lymphoma, CNB is performed, with or without FNA, at the discretion of the ordering physician and radiologist. In both groups of patients, performing CNB alone may decrease the procedure time and cost, potentially leading to improved patient satisfaction while maintaining a similar diagnostic yield.

Core needle biopsy without FNA of peripheral lymph nodes provides sufficient tissue to obtain an actionable diagnosis in new or recurrent lymphoma. However, discussions with our pathologists reveal that flow cytometric data from FNA may decrease the special stains necessary for processing of CNB specimens, potentially improving pathology work flow. Our institutional practice is to submit FNA for flow cytometry, but CNB specimens in RPMI solution could be submitted for this purpose, streamlining the work flow for both pathology and radiology.

References


