Surgical Biopsy of Pathologically Enlarged Lymph Nodes: A Reappraisal

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ABSTRACT: **Background:** Enlarged lymph nodes (ELN) pose a great diagnostic challenge. They may represent the first clinical finding of a hematologic disease or other malignancy and may be an indication of a wide range of infectious and non-infectious diseases. Because many patients undergo percutaneous biopsy, surgical excisional biopsy is not often considered.

Objectives: To analyze indications for a patient's referral for surgical biopsy of ELN and diagnostic steps to follow until referral, and to determine the number of ELN.

Methods: A retrospective study was conducted of prospectively collected data from patients who underwent surgical biopsy of ELN from January 2004 to December 2013.

Results: Of 118 patients who underwent surgical biopsy of ELN, only 52 (44%) had a needle biopsy (NB) before referral. Lymphoma was diagnosed by NB in 24 (46%) of the referred patients. In patients with a previous diagnosis of lymphoma, NB of ELN yielded a sensitivity of 67% and specificity of 79%. In patients with lymphadenopathy but with no previous history of malignancy, sensitivity for lymphoma was 68% and specificity was 71%. The investigative time period until final diagnosis was 3 months in patients who had NB but only 1.25 months in patients who were referred directly for surgery ($P < 0.0001$).

Conclusions: Surgical biopsy of ELN still has a place in the clinical evaluation of patients with ELN. Surgery may significantly reduce the length of investigation and prevent unnecessary diagnostics, especially in patients with suspected lymphoma recurrence.

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KEY WORDS: enlarged lymph nodes (ELN), lymphadenopathy, lymphoma, percutaneous biopsy

Enlarged lymph nodes (ELN) are sometimes the first clinical finding of an illness, specifically of hematologic origin. A surgical lymph node biopsy for the purpose of diagnosis is occasionally required.

Currently, ultrasound or computed tomography (CT)-guided biopsies are the gold standard for tissue sampling because they are minimally invasive procedures that are associated with low morbidity and an acceptable diagnostic yield [1-3]. In some circumstances, tissue extraction via core needle biopsy is not adequate or tissue architecture is ruined and therefore diagnosis cannot be established [3,4]. If that is the case, surgical biopsy is scheduled. Patients often wait substantially long periods of time for a biopsy and consequently diagnosis is deferred and treatment is delayed. Furthermore, a large percentage of patients undergo more than one core needle biopsy before eventually requiring surgical biopsy to make a final diagnosis. Although some patients who undergo surgical biopsy show no specific pathology and do not require explicit treatment, it is nevertheless important to improve patient pathways of care to allow for the delivery of timely and appropriate treatment. We analyzed the pathways of care for patients referred for surgical diagnostic lymph node biopsy at our institute.

PATIENTS AND METHODS

The study was a retrospective cohort analysis of all patients who underwent surgical biopsy of for ELN at the general surgery department at the Rambam Health Care Campus, Haifa, Israel, from January 2004 to December 2013. The files of all patients who underwent surgical biopsy of lymph nodes to aid diagnosis were collected from computerized hospital records. Patients were excluded if surgical lymph node biopsy or dissection was performed as part of staging surgical procedures. Data collected from the prospective database included patient demographics, preoperative diagnoses, laboratory and imaging evaluations, preoperative pathological needle biopsy results, and the anatomical site of the previous biopsy. Data about the surgical lymph node biopsy included the site and final pathological results as well as the elapsed period until surgical biopsy. The study was approved by the ethics committee of the Rambam Health Care Campus.

STATISTICS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics in terms of mean, standard deviation, median, and percentiles were applied to all parameters in the study. Fisher's exact test was used to determine differences between categorical param-

eters. Diagnostic measurements using sensitivity and specificity statistics were conducted to assess how often the preoperative pathological needle biopsy diagnostic results agreed with those from the final surgical lymph node biopsy. Mann–Whitney U test was used for demonstrating differences among groups. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 118 patients underwent a diagnostic surgical lymph node biopsy during the study period. The most common indication for surgical biopsy was lymphadenopathy, which was reported in 54 (46%) patients. Other reasons for initiating investigations included a previous history of lymphoma in 31 patients (26.3%), fever of unknown origin (FUO) in 14 patients (12%), and a history of cancer in 6 patients (5%). Twelve patients (10%) presented with nonspecific symptoms, and one patient was diagnosed with human immunodeficiency virus (HIV). Patient demographics and main indications for referral are shown in Table 1.

Table 1. Patient demographics and indications for referral

		N (%)
Patient demographics	Male Female Age in years, mean ± standard deviation (range 18–83)	65 (55.1) 53 (44.9) 49 ± 18
Indications for referral	Lymphadenopathy Lymphoma FUO Nonspecific symptom Cancer HIV	54 (46) 31 (26.3) 14 (12) 12 (10) 6 (5) 1 (0.8)
Clinical investigations	Chest X-ray CT scan Ultrasound examination EUS PET/CT MRI BMB Blood tests	97 (82.2) 72 (61) 65 (55.1) 4 (3.4) 44 (37.3) 7 (5.9) 36 (30) 118 (100)
Reason for surgery without previous needle biopsy	Lymphadenopathy Lymphoma history Nonspecific symptom FUO Cancer history	31 (47) 13 (19.7) 11 (16.7) 10 (15.2) 1 (1.5)
Reason for needle biopsy before surgery	Lymphadenopathy Lymphoma history Nonspecific symptom FUO Cancer history HIV	23 (44.2) 18 (34.3) 1 (1.9) 4 (7.7) 5 (9.6) 1 (1.9)
Pathology revealed by needle biopsy	No pathology Lymphoma Non-diagnostic Granulomatous infection	15 (29) 24 (46) 12 (23) 1 (2)

BMB = bone marrow biopsy, CT = computed tomography, EUS = endoscopic ultrasound, FUO = fever of unknown origin, HIV = human immunodeficiency virus, MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography

PERCUTANEOUS NEEDLE BIOPSIES

Prior to being referred for surgical lymph node biopsy, the patients underwent a wide range of investigations [Table 1]. Sixty-six patients (56%) were sent for surgery after investigations without any attempt at percutaneous biopsies. In these cases, the indications were lymphadenopathy in 47% of patients, previous history of lymphoma in 19.7%, nonspecific symptoms in 16.7%, FUO in 15.2%, and a history of cancer in 1.5%.

Fifty-two patients (44.1%) underwent percutaneous biopsy prior to surgical consultation. Reasons included lymphadenopathy in 44.2% of patients, previous history of lymphoma in 34.6%, history of cancer in 9.6%, and FUO in 3.8%. One patient presented with nonspecific symptoms and one had been diagnosed with HIV.

Of the 52 patients who underwent percutaneous biopsy 75% experienced one attempt at the procedure, 9 patients (17%) endured two attempts, and 4 patients (7.7%) underwent more than two biopsies. The distribution of the site of percutaneous biopsy was inguinal in 38% (20/52), axillary in 23% (12/52), intraperitoneal in 23% (12/52), cervical in 17% (9/52), and other sites in 4% (2/52) of patients. Twenty-four (46%) of these 52 patients were diagnosed with new lymphoma, while in 12 patients (23%) the pathologic result was non-diagnostic. One patient's pathology showed granulomatous infection, while 29% of patients showed no identifiable pathology [Table 1]. No statistical difference was found in patients who underwent percutaneous biopsy before surgery and those who did not, with regard to disease history.

SURGICAL LYMPH NODE BIOPSIES

The anatomical distribution of the excised lymph nodes is detailed in Table 2. The most common locations for lymphadenopathy were inguinal in 39.8% and axillary in 32.2% of patients. Of the 118 patients, the dominant histopathology diagnosis from surgical biopsy was lymphoma in 48 (40.7%). Other findings of surgical biopsy included nonspecific lymphadenopathy in 32 (27.1%), specific nontuberculous lymphadenitis in 29 (24.6%), tuberculous lymphadenitis in 3 (2.5%), metastatic lymphadenopathy in 2 (1.7%), non-diagnostic in 1 (0.8%), and leukemia in 1% of patients [Table 3].

Table 2. Anatomical distribution of the surgical lymph nodes biopsies

Anatomical Site	N (%)
Axilla	38 (32.2)
Inguinal	47 (39.8)
Intraperitoneal	23 (19.5)
Cervical	8 (6.8)
Thigh	1 (0.8)
Hand	1 (0.8)
Total	118 (100)

Table 3. Histology of surgical lymph node biopsy

Diagnosis	N (%)
Lymphoma	48 (40.7)
Nonspecific lymphadenopathy	32 (27.1)
Specific nontuberculous lymphadenitis*	29 (24.6)
Tuberculous lymphadenitis	3 (2.5)
Metastatic lymphadenopathy	2 (1.7)
Non-diagnostic	1 (0.8)
Total leukemia	118 (100)

*sarcoidosis, toxoplasmosis, systemic lupuserythematosus lymphadenopathy, foreign body reaction, abscess, infectious mononucleosis, cat scratch disease, granulomatous inflammation (nondiagnostic), toxoplasmosis

SENSITIVITY AND SPECIFICITY

The sensitivity and specificity of percutaneous biopsy for diagnosis of lymphoma in all subgroups of patients were 67.8% and 79%, respectively, with a false positive rate in 21% (5/24) and false negative rate in 32% (9/28) of patients [Table 4]

Fifty-four patients (46%) were referred for surgical biopsy due to lymphadenopathy only. Of this group, a histological result of lymphoma from excisional biopsy occurred in 18 cases (35% of all patients). The sensitivity and specificity of percutaneous biopsy for diagnosis of lymphoma, in patients who were sent for examination due to lymphadenopathy only, were 53.8% and 70%, respectively, with a false positive rate in 30% and a false negative rate in 46% of patients.

Overall, 31 patients (26.3%) had a previous history of lymphoma. Eighteen of these patients (58%) underwent percutaneous biopsy. In seven patients (22%), the biopsy revealed a recurrence of lymphoma. Surgical biopsy confirmed the diagnosis of lymphoma in only five patients (71.4%). The sensitivity and specificity of percutaneous biopsy for diagnosis of recurrence of lymphoma were 62.5% and 80%, respectively, with a false positive rate of 28.5% and a false negative rate of 27%. The results did not reach statistical significance due to the small numbers of patients in these two groups.

The sensitivity and specificity of the fine needle biopsy (FNB) was tested separately for identifiable lymphoma pathology in all groups of patients and were found to be 63% and 82%, respectively. The results were thus not much different from a combined result of fine needle aspiration (FNA) and FNB.

The median time from starting the investigation until obtaining final diagnosis was 3 months in patients who had undergone percutaneous biopsy, but only 1.25 months in patients who were referred directly for surgery ($P < 0.0001$).

Table 4. Sensitivity and specificity of percutaneous biopsy for lymphoma

	Sensitivity (%)	Specificity (%)	False positive (%)	Negative predictive value (%)	*P* value
All patients* N=52	19/28 (67.8)	19/24 (79)	5/24 (21)	9/28 (32)	0.0009
Lymphoma patients** n=18	5/8 (62.5)	8/10 (80)	2/7 (28.5)	3/11 (27)	0.15
Lymphadenopathy*** patients n=23	7/13 (53.8)	7/10 (70)	3/10 (30)	6/13 (6)	0.40

*All patients who underwent a percutaneous biopsy prior to surgery

**Patients with lymphoma history who underwent a percutaneous biopsy prior to surgery

***Patients with lymphadenopathy in presentation who underwent a percutaneous biopsy prior to surgery

DISCUSSION

In common practice it is rare to base a diagnosis on the results of excisional biopsy of ELN. This practice is due to the development of new methods of percutaneous biopsy and the advent of more accurate techniques. Nevertheless, surgical biopsy allows for the extraction of lymph nodes to permit a more detailed pathological analysis. Preserving lymph node microarchitecture and harvesting large samples aids in the final pathological diagnosis as well as permits thorough tissue workup. Excisional biopsy presented a diagnosis in 71% of the patients in our data sample. This result is in line with the overall diagnostic yields of surgical biopsy of 70.4% and 63% that were first described 30 years ago by Doberneck [5] and Margolis and their teams [6], respectively.

In the general population, the incidence of malignant neoplasms that are determined following a presentation of lymphadenopathy is very low [7-9]. However, this is not the case among patients undergoing investigation at medical centers where the proportion of patients receiving a diagnosis of malignant tumors reaches 40–60% [10]. In our study, lymphoma was the most common diagnosis obtained by both percutaneous biopsies (in 46% of patients) and surgical biopsies (in 40.7% of patients). Morris-Stiff and colleagues [11] found that lymphoma is a common cause of lymphadenopathy, representing the histological diagnosis in 21% of all lymph node biopsy specimens. Moor et al. [12] reported a surgical diagnosis of lymphoma in 19% of all cases including adults and children. The higher percentage of lymphoma diagnoses by surgical pathology in the present study is likely explained by the high number of patients who were referred already with a previous history of lymphoma and the clinical suspicion of disease recurrence. This finding may also suggest a reflection of a very busy hematological diseases center, as in our institution.

A substantial proportion of patients undergoing surgical biopsy show findings that do not require treatment. Indeed, our study found that 21.7% of all lymph node biopsies showed non-specific lymphadenopathy not requiring further treatment. Moor's team [12] recorded 45% of cases with non-specific lymphadenopathy not requiring further treatment, raising the question about whether this diagnosis could have been made on other, non-surgical grounds.

Surgical biopsy is considered a minor procedure involving procurement and study of tissue for the purpose of diagnosis,

although with the drawbacks of being neither inexpensive nor free of morbidity. In more recent years, guided biopsies have become the gold standard for tissue sampling since they are cost-effective and involve a simple and minimally invasive procedure that is associated with low morbidity. These procedures may provide rapid information and direct approach when facing a patient presenting with lymphadenopathy. Guided biopsies can be used on palpable or non-palpable lymph nodes. In the latter case, different techniques can be used, such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and abdominal or thoracic CT-guided biopsy. Needle biopsy is quick, does not require a general anesthetic, can be performed ambulatory, and has high overall sensitivity and specificity with low false-negative and false-positive results [13-18].

In our study, 52 patients (44.1%) underwent percutaneous biopsy prior to surgical consultation. Of these, 33 underwent core-needle biopsy (FNB) only, 16 both FNA and FNB, and 3 FNA only. Since the most common pathologic diagnosis was lymphoma, we decided to review the sensitivity and specificity of percutaneous biopsy for detection of lymphoma. Our results contrast the published literature, which reported higher sensitivity and specificity of percutaneous core-needle biopsy for the diagnosis of lymphoma with fewer false positive and negative case results [1,19,20]. Demharter and co-authors [21] showed that 135 FNB procedures for the diagnosis of lymphomas had just two false-positive and seven false-negative biopsy results, corresponding to a sensitivity of 89% and a specificity of 97%. Some studies have shown that FNA has a lower sensitivity than FNB in the diagnosis of lymphoma. However, the use of FNA may be important in special cases in which patients have cervical lymphadenopathy so that squamous carcinoma metastases from the head and neck can be excluded. This procedure is primarily performed because an open biopsy leads to a significantly higher local treatment failure rate, which may in turn be associated with an adverse effect on survival [22]. The differences observed may be related to technique and sample size as well performer expertise. The investigation of exact reasons is beyond the scope of the current study.

The duration spent on investigations is important and may affect timing of proper treatment. Often such investigation periods are lengthy with patients waiting a substantial time for biopsy, thus resulting in deferred diagnosis and delayed treatment. A large percentage of patients undergo more than one biopsy before surgical biopsy and eventual final diagnosis. We observed that a quarter of the patients who underwent percutaneous biopsy had had more than one biopsy attempt. Our results are particularly noteworthy if we consider that every additional attempt to repeat a biopsy, including its associated waiting time, causes patients further anxiety and frustration, negatively affecting their quality of life.

CONCLUSIONS

Surgical lymph node biopsy, if performed correctly, is likely to yield an optimal diagnostic result. However, in view of the invasive nature of the procedure, such biopsies should be undertaken only in patients with a definitive indication or with a high suspicion for lymphoma. The first percutaneous biopsy result can be uninformative, especially in patients with a history of lymphoma; however, occasionally the type of lymphoma cannot be accurately determined. In these situations, repeated percutaneous biopsies should be avoided and patients should be referred for surgery.

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Capsule

Some (re)programming notes on cancer

Epithelial cancers develop resistance to targeted therapies in a number of different ways. Several cancer types do so by undergoing phenotypic conversion to a highly aggressive cancer called small cell neuroendocrine carcinoma (SCNC). Whether distinct cancer types accomplish this "reprogramming" through the same mechanism has been unclear. **Park** et al. showed that the same set of oncogenic factors transforms both normal lung and normal prostate epithelial cells into SCNCs that resemble clinical samples. This convergence of molecular pathways could potentially simplify the development of new therapies for SCNC, which is currently untreatable.

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Eitan Israeli

Capsule

Gene for preeclampsia

Preeclampsia is a serious complication of pregnancy that often presents as an increase in maternal blood pressure. The disorder is more prevalent and severe in women with African ancestry, most likely because of genetic factors. **Reidy** and colleagues investigated a variant of the gene encoding apolipoprotein L1 *(APOL*1), which was previously shown to confer a high risk of kidney disease in black Americans. Studying two independent populations of pregnant black women, they found that preeclampsia was associated with the *APOL*1 high-risk genotype. Interestingly, it was the genotype of the fetus, not the mother, that mattered. The fetal *APOL*1 high-risk genotype may be linked to one in eight cases of preeclampsia in black women.

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Eitan Israeli

Capsule

Necroptosis microenvironment directs lineage commitment in liver cancer

Primary liver cancer represents a major health problem. It comprises hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), which differ markedly with regards to their morphology, metastatic potential, and responses to therapy. However, the regulatory molecules and tissue context that commit transformed hepatic cells toward HCC or ICC are largely unknown. **Seehawer** and colleagues showed that the hepatic microenvironment epigenetically shapes lineage commitment in mosaic mouse models of liver tumorigenesis. Although a necroptosis-associated hepatic cytokine microenvironment determines ICC outgrowth from oncogenically transformed hepatocytes, hepatocytes containing identical oncogenic drivers give rise to HCC if they are surrounded by apoptotic hepatocytes. Epigenome and transcriptome profiling of mouse HCC and ICC singled out *Tbx*3 and *Prdm*5 as major microenvironment-dependent and epigenetically regulated lineage-commitment factors, a function that is conserved in humans. Together, these results provide insight into lineage commitment in liver tumorigenesis, and explain molecularly why common liver-damaging risk factors can lead to either HCC or ICC.

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Eitan Israeli

"Inaction saps the vigor of the mind"

Leonardo da Vinci, (1452–1519), Italian Renaissance scientist, mathematician, engineer, inventor, anatomist, painter, sculptor