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Original Scientific Paper

ANALYSIS OF DIAGNOSTIC EXCISIONAL LYMPH NODE BIOPSY RESULTS: 12-YEAR EXPERIENCE OF A SINGLE CENTER

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SUMMARY – Lymph node biopsy is indicated in patients with suspected malignancy or lymphadenopathy due to unclarified reasons. Lymph node biopsy can be performed as fine needle aspiration biopsy, core biopsy, or excisional lymph node biopsy. In particular, the diagnosis of malignant lymphoma is considered insufficient for oncological treatment unless classified into subgroups. Core biopsy and excisional biopsy can be performed to diagnose lymphoma and classify it into subgroups. Core biopsy may also be limited in some cases for the diagnosis of lymphoma. Therefore, patients are referred to surgical departments for excisional lymph node biopsy. It was aimed herein to analyze the results of excisional lymph node biopsies performed for diagnostic purposes in our department. Data on 73 patients having undergone diagnostic excisional lymph node biopsy at Sakarya University Medical Faculty Training and Research Hospital between January 2008 and January 2020 were retrospectively analyzed. Patients were evaluated in terms of age, gender, biopsy site, pathological diagnosis, number and diameter of lymph nodes excised. Patients younger than 18 years of age, those with sentinel lymph node biopsies, and lymph node dissections performed for any known malignancy were excluded from the study. Statistical data analysis was done using SPSS statistical software. There were 37 (50.7%) female and 36 (49.3%) male patients, mean age 52.07 (18-90) years. Axillary lymph node biopsy was performed in 32 patients, inguinal lymph node biopsy in 29 patients, cervical lymph node biopsy in 3 patients, intra-abdominal lymph node biopsy in 6 patients, mediastinal lymph node biopsy in 1 patient, and supraclavicular lymph node biopsy in 2 patients. All of the lymph node biopsies were performed as excisional biopsy. Malignancy was detected in 36 (49.3%) patients. In 37 (50.3%) patients, the causes of lymphadenopathy were found to be benign pathologies. When the causes of malignant disease were examined, it was observed that 23 (31.5%) patients were diagnosed with lymphoma. Hodgkin lymphoma was detected in 5 patients diagnosed with lymphoma, and non-Hodgkin lymphoma was found in 18 patients. Metastatic lymphadenopathy was observed in 13 (17.8%) patients. Reactive lymphoid hyperplasia (26%) and lymphadenitis (20.5%) were found among the causes of benign lymphadenopathy. The number of excised lymph nodes was between 1 and 4, and their diameter was between 9 and 75 mm (mean: 29.53±15.56 mm). There was no statistically significant difference between benign and malignant patients according to gender, age, lymph node diameter, number of lymph nodes excised, and excisional lymph node biopsy site. For diagnostic lymph node biopsy, fine-needle aspiration biopsy and core biopsy should be performed primarily. If lymphoma is suspected in the diagnosis, fine-needle aspiration biopsy is not necessary. In this case, it is believed that it is more appropriate to perform core biopsy first. If the core biopsy is insufficient for diagnosis, it is more appropriate to perform surgical biopsy in order to cause no delay in diagnosis and treatment. Excisional biopsy is a method that can be safely performed and does not cause severe morbidity in palpable peripheral lymphadenopathies. Although it does not cause severe morbidity because it is an invasive procedure, excisional biopsy should be performed in a selected patient group.

Key words: *Lymphadenopathy; Excisional biopsy; Lymphoma; Reactive lymphoid hyperplasia; Lymphadenitis*

Introduction

An increase in the lymph node size and an abnormal change in its structure are defined as lymphadenopathy. Generally, a lymph node larger than 1 cm or

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smaller but numerous is considered abnormal[1]. The site where lymphadenopathy is formed is equally important. For example, an isolated inguinal lymph node may rarely be related to malignancy, while the palpable supraclavicular, iliac, or popliteal lymph nodes may be suspicious[1]. Lymphadenopathy occurs due to the proliferation of neoplastic or inflammatory cells in the lymph node or invasion of the lymph node. Enlarged lymph nodes may sometimes be the first clinical sign of a disease, especially a disease of hematologic origin. In patients with suspected malignancy or lymphadenopathy due to unclarified reasons, lymph node biopsy is indicated for diagnosis. Currently, ultrasound- or computerized tomography-guided biopsies are the gold standard for tissue sampling as they are minimally invasive procedures associated with low morbidity and an acceptable diagnostic yield[2,3]. Therefore, these minimally invasive procedures are also the first choice for lymph node biopsies. However, in some cases, tissue extraction with core biopsy may not be adequate, or the tissue structure may be impaired in the sample taken and therefore, undiagnosed [3,4]. In this case, surgical biopsy is planned.

Furthermore, a large percentage of patients will have more than one core biopsy and then require surgical biopsy for definitive diagnosis. These patients often wait considerably longer for biopsy, and consequently, diagnosis and treatment will be delayed.

Patients who cannot be diagnosed with percutaneous biopsy methods, especially those with a suspected malignant lymphoproliferative disease, are referred to surgical departments for excisional biopsy. Therefore, it was aimed herein to evaluate the results of excisional lymph node biopsies performed for diagnostic purposes in our department.

Material and Method

Data on 73 patients having undergone diagnostic excisional lymph node biopsy at Sakarya University Medical Faculty Training and Research Hospital between January 2008 and January 2020 were retrospectively analyzed. The patient group included those referred to the General Surgery Department for direct excisional biopsy by the Hematology Department and those that underwent excisional biopsy in our department. These patients were those who were not suitable for core biopsy or who had undergone core biopsy but had not obtained satisfactory results.

Study patients were evaluated in terms of age, gender, biopsy site, pathological diagnosis, number, and diameter of the lymph nodes excised. These parameters were compared separately between the benign and malignant patient groups. Patients younger than 18 years of age, those who had sentinel lymph node biopsies and lymph node dissections performed due to any known malignancy were excluded from the study.

Approval for the present study was obtained from the Ethics Committee of the Sakarya University Faculty of Medicine (71522473/050.01.04/6056/34).

Statistical analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distribution of numerical variables was normal. Accordingly, Student's t-test for parametric independent numerical variables and Mann-Whitney U test for nonparametric numeric independent variables were used to compare the groups. The parametric numerical variables were presented as mean ± standard deviation, and the nonparametric numerical variables were presented as median (min-max). Categorical variables were compared using the χ^2-test. Categorical variables were presented as numbers and percentages. The level of statistical significance was set at $p<0.05$. Analyses were performed using IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA).

Results

There were 37 female and 36 male patients, mean age 52.07 (18-90) years. Axillary biopsy was performed in 32 patients, inguinal in 29 patients, cervical in 3 patients, intra-abdominal in 6 patients, mediastinal in 1 patient, and supraclavicular lymph node biopsy in 2 patients. Malignancy was detected in 36 (49.3%) patients. In 37 (50.7%) patients, the causes of lymphadenopathy were found to be benign pathologies.

When the causes of malignant disease were evaluated, 23 patients were diagnosed with lymphoma (Table 1). Hodgkin lymphoma was found in 5 patients who were diagnosed with lymphoma, and non-Hodgkin lymphoma was found in 18 patients. According to the non-Hodgkin lymphoma subtypes, 5 patients had small lymphocytic, 5 had diffuse large B-cell lymphoma, 3 had nodal marginal zone, and 5 had B-cell lymphoma. Metastatic lymph nodes were

Table 1. Patients diagnosed with malignancy as a result of excisional biopsy

Malignant lymphadenopathy		
Lymphoma		23 (31.5%)
	Non-Hodgkin lymphoma	18
	Hodgkin lymphoma	5
Carcinoma metastasis		10 (13.6%)
Epithelioid angiosarcoma		1 (1.36%)
Malignant melanoma metastasis		1 (1.36%)
Seminoma metastasis		1 (1.36%)
Sum of malignant lymphadenopathy and ratio among lymph node biopsies		36 (49.3%)

observed in 13 patients. Small cell lung carcinoma, endometrioid adenocarcinoma, malignant melanoma, epithelioid angiosarcoma, and seminoma metastases were observed in 5 of these 13 patients, one each. Merkel cell carcinoma was observed in 2 patients. Primary cancer could not be identified in other metastatic lymph nodes.

Among benign patients, 19 had reactive lymphadenopathy. Of the patients diagnosed with lymphadenitis, 2 had caseous necrotizing granulomatous lymphadenitis (tuberculous lymphadenitis), 2 had necrotizing granulomatous lymphadenitis, 2 had non-necrotizing granulomatous lymphadenitis, and 9 had chronic lymphadenitis. Langerhans cell histiocytosis was observed in 1 patient and dermatopathic lymphadenopathy in 2 patients (Table 2).

Of the patients, 49 had accompanying generalized lymphadenopathy. The number of excised lymph nodes was between 1 and 4, and their mean diameter was 29.53 (±15.56) mm. All of the intra-abdominal excisional biopsies were performed laparoscopically. While patients who underwent laparoscopic excisional biopsy were hospitalized for 1 day, other patients were discharged on the same day of the procedure.

There was no statistically significant difference between the benign and malignant patient groups according to gender, age, lymph node diameter, number of excised lymph nodes and lymph node site (Table 3).

Table 2. Patients diagnosed as benign as a result of excisional biopsy

Benign lymphadenopathy	
Reactive lymphoid hyperplasia	19 (26%)
Lymphadenitis	15 (20.5%)
Langerhans cell histiocytosis	1 (1.36%)
Dermatopathic lymphadenopathy	2 (2.74%)
Sum of benign lymphadenopathy and ratio among lymph node biopsies	37 (50.7%)

Table 3. Comparison of various parameters in benign and malignant patient groups

		Benign	Malignant	p-value
Gender	Female	21 (28.8%)	16 (21.9%)	0.20
	Male	16 (21.9%)	20 (27.4%)	
Age		51.2±17.06	52.9±14.7	0.66
Number of lymph nodes removed		2 (1-4)	1.5 (1-4)	0.82
Mean lymph node diameter		27.89±13.74	31.22±17.26	0.64
Removed lymph node site				0.33
	Neck	1	2	
	Supraclavicular	0	2	
	Axilla	15	17	
	Inguinal	18	11	
	Mediastinal	0	1	
	İntra-abdominal	3	3	
All patients		37 (50.7%)	36 (49.3%)	

Discussion

Lymphadenopathy occurs due to various conditions, such as infectious, immune or neoplastic diseases, and metabolic disorders, as well as drug or iatrogenic causes[5,6]. Generally, lymph nodes smaller than 1 cm in diameter are considered benign. However, when the size of the lymph node is more than 2 cm, it often suggests malignancy or a granulomatous disease[1,7]. Therefore, biopsy should be performed if the size of lymphadenopathy increases rapidly within 2 weeks and does not shrink within 4-6 weeks and does not entirely regress in 8-12 weeks[8].

Fine needle aspiration biopsy is valuable for distinguishing benign and malignant lesions, but the lack of adequate material for diagnosis is an important issue. Moreover, in order to initiate oncologic treatment in malignancies such as lymphoma, the subgroup of malignancy should be determined. Core biopsy is also valuable for determining the subgroups of malignancies such as lymphoma. Core biopsy performed instead of excisional lymph node biopsy for lymph nodes that are located deep in the mediastinum or abdomen, which is difficult to reach, reduces patient morbidity and hospital stay, and provides significant advantages[9,10]. In recent years, the role of percutaneous biopsies in lymphoproliferative diseases has gained importance with advances in biopsy, histopathology, and immunohistochemistry techniques[11]. However, there are situations in which core biopsy is insufficient or false negative. In these cases, excisional biopsy should be considered for diagnosis[11,12]. Therefore, our patient group mainly consisted of those who were not suitable for core biopsy or were referred from Internal Medicine and Hematology Departments, in whom core biopsy was applied, but no result was obtained. For this reason, all the patients that underwent lymph node biopsy were those that underwent excisional biopsy.

Excisional lymph node biopsy is a very effective method, especially in determining the subgroups of lymphoma. Excisional lymph node biopsies should be performed from easily palpable superficial areas, such as the axillary region, inguinal region, or neck. If there are no palpable superficial lymph nodes, excision can also be made from deep lymphadenopathy sites. While laparoscopy may be performed for excisional intra-abdominal lymph node biopsies, mediastinoscopy may be performed for mediastinal lymph node biopsies. On the other hand, it is recommended not to opt for incisional biopsy in patients scheduled for surgical biopsy. The possibility that lymph fluid accumulating at the wound site after incisional biopsy may lead to

wound infection and lymphatic fistula should be kept in mind[13]. It is more likely that a fistula will emerge following incisional biopsy performed for tuberculous lymphadenopathy, and therefore it is considered contraindicated[14]. In the series herein, no serious surgical complication developed in any of the patients having undergone excisional biopsy. In addition, incisional biopsy was not performed in any of the patients.

In the current study, the malignancy rate was 49.3%. In a study by Pannick *et al.*, 26 (43%) of the 60 patients whose data were analyzed had malignancies[15]. In a study conducted by Darnal *et al.*, malignancy was observed in 47% of 273 adult patients who underwent surgical lymph node biopsy[16]. In the current study, the rate of malignancy was close to those reported in these studies. On the other hand, Özkan *et al.* detected malignancy in 123 (66.5%) of 185 patients in their study[1]. In another study conducted by Moor *et al.*, malignancy was detected in 117 (34%) of 342 patients[17]. As can be seen, the malignancy rates varied in various studies.

In the study herein, lymphomas were the most common cause in the malignant lymphadenopathy patients. Non-Hodgkin lymphoma was seen in 18 (24.6%) and Hodgkin lymphoma in 5 (6.8%) patients. In a study performed by Gul *et al.*, in which excisional lymph node biopsies were evaluated, they found non-Hodgkin lymphoma in 11 (16.4%) and Hodgkin lymphoma in 7 (10.4%) patients[13]. In the same study, metastatic lymph nodes were detected in 5 (7.5%) patients, whereas in the current study, they were detected in 13 (17.8%) patients. In another study conducted by Dorfman *et al.*, it is reported that 40.7% of the 118 patients who underwent surgical biopsy were diagnosed with lymphoma[3]. In another study by Sheresta *et al.*, lymphoma was found in only 7 (5.3%) of the 132 patients who underwent excisional lymph node biopsy[18]. It is believed that these differences in the results are due to the high incidence of tuberculous lymphadenopathy in the etiology in endemic regions.

It has been stated that the possibility of malignancy is higher in supraclavicular and neck lymphadenopathy[19]. Consistent with this study, malignancy was reported in 2 patients in whom supraclavicular lymph node excisional biopsy was performed and 2 of 3 patients in whom cervical lymph node excisional biopsy was performed. Moreover, lymphadenopathy occurring in the inguinal region had a relatively lower malignancy probability[18,19]. In accordance with the literature, malignancy was detected in 11 of the 29 inguinal region lymph node biopsies performed.

Although it has been emphasized in various studies that there is a diameter difference between malignant and benign lymph nodes, no statistically significant difference was observed in the study herein. In another study, it was found that the mean diameter of malignant lymph nodes was 40 mm *versus* mean diameter of benign lymph nodes of 25 mm in patients who underwent excisional lymph node biopsy, and this diameter difference was statistically significant[13]. In another study by Kılıcarslan *et al.*, the mean benign lymphadenopathy diameter was found to be 26.1 mm, while the mean malignant lymphadenopathy diameter was 35.6 mm. Furthermore, in this study, there was no statistically significant difference between benign lymphadenopathy patients and malignant lymphadenopathy patients, as in the current study ($p>0.05$)[20].

When the lymph node biopsy results herein were evaluated, it was determined that reactive lymphoid hyperplasia was most common among the benign lymphadenopathy patients. Reactive lymphoid hyperplasia is a condition that is thought to be due to repetitive antigenic stimulation encountered in childhood and young ages and is a common cause of lymphadenopathy in the adult age group (20%-30%)[21]. Reactive lymphoid hyperplasia was observed in 19 (26%) patients, with rates similar to the literature. Tuberculous lymphadenitis is the most common type of lymphadenopathy in some endemic geographical regions such as Africa and southern Asia[18,22]. In contrast to the results obtained in endemic regions in the current series, tuberculous lymphadenitis was observed in 2 (2.7%) patients. Dermatopathic lymphadenopathy is also a rare and benign condition in which pigment-containing macrophages exist in lymph nodes that develop on the basis of various skin diseases[23]. In the current series, it was seen at a rate of 2.7% (2 patients). The benign lymphadenopathy results showed results similar to some other studies[3,24].

It is recommended to target the lymph node that appears to be most abnormal among the lymph nodes available for excisional biopsy, even if it is not the easiest to access[18]. Excisional biopsy for palpable peripheral lymphadenopathy is a method that can be performed safely and often does not cause severe morbidity[25]. In addition, a definitive diagnosis result is expected with excisional biopsy. No severe morbidity was observed in the study patients after excisional biopsy, and be-

nign and malignant differentiation could be made in all of the patients. Although it does not cause severe morbidity, excisional biopsy should be performed in a selected patient group because it is an invasive procedure.

It was believed herein that it would be more appropriate to perform lymph node biopsy primarily with core biopsy in centers with an interventional radiology department.

The limitations of this study were its retrospective nature and the small number of cases.

In conclusion, diagnostic lymph node biopsies should be performed as core biopsy primarily. If core biopsy is insufficient for diagnosis, the surgical biopsy option should come to the forefront. If the diagnosis is not made after the first percutaneous biopsy, it is recommended to perform excisional biopsy in order to cause no delay in diagnosis. With the advances in core biopsy and subsequent histopathologic and immunohistochemical examination techniques, it is believed that in the future, more core biopsy will be performed, mainly in difficult-located lymphadenopathy patients. Further studies with a high number of cases comparing core biopsy and excisional biopsy are needed. However, excisional biopsy is a method that can be performed safely and does not cause severe morbidity in palpable peripheral lymphadenopathy. Incisional biopsy should be avoided whenever possible because of its potential to cause wound infection and lymphatic fistula. It is recommended to perform excisional biopsies with the laparoscopic approach in the presence of intra-abdominal lymphadenopathy.

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Sažetak

ANALIZA REZULTATA DIJAGNOSTIČKE EKSCIZIJSKE BIOPSIJE LIMFNIH ČVOROVA: 12-GODIŠNJE ISKUSTVO JEDNOG CENTRA

Z. Bayhan, K. Ozdemir, E. Gonullu, A. T. Harmantepe, R. Capoglu, E. Akin, M. Aziret i *F. Altintoprak*

Biopsija limfnih čvorova indicirana je u bolesnika sa sumnjom na zloćudnu bolest ili s limfadenopatijom nejasnog uzroka. Biopsija limfnih čvorova može se izvesti kao tankoiglena aspiracijska biopsija, širokoiglena biopsija ili ekscizijska biopsija limfnih čvorova. Dijagnoza zloćudnog limfoma smatra se naročito nedostatnom za onkološko liječenje ako nije provedena klasifikacija u podskupine. Širokoiglena biopsija i ekscizijska biopsija mogu se provesti kako bi se dijagnosticirao limfom i klasificirao u podskupine. Širokoiglena biopsija može se također u nekim slučajevima pokazati ograničenom u dijagnosticiranju limfoma. Zato se bolesnici upućuju u kirurške odjele na ekscizijsku biopsiju limfnih čvorova. Cilj ovoga istraživanja bio je analizirati rezultate ekscizijskih biopsija limfnih čvorova izvedenih u dijagnostičke svrhe na našem odjelu. Retrospektivno su analizirani podaci za 73 bolesnika podvrgnutih dijagnostičkoj ekscizijskoj biopsiji limfnih čvorova u Sveučilišnoj bolnici Sakarya između siječnja 2008. i siječnja 2020. godine. Analizirani su sljedeći podaci: dob, spol, mjesto gdje je izvedena biopsija, patološka dijagnoza, broj i promjer ekscidiranih limfnih čvorova. Iz istraživanja su bili isključeni bolesnici mlađi od 18 godina, oni s biopsijom *sentinel* limfnih čvorova te oni s disekcijom limfnih čvorova zbog bilo kakve poznate zloćudne bolesti. Statistička analiza podataka provedena je pomoću statističkog programa SPSS. Bilo je 37 (50,7%) ženskih i 36 (49,3%) muških bolesnika srednje dobi od 52,07 (18-90) godina. Biopsija aksilarnih limfnih čvorova izvedena je u 32, ingvinalnih limfnih čvorova u 29, cervikalnih limfnih čvorova u 3, intra-abdominalnih limfnih čvorova u 6 bolesnika, mediastinalnih limfnih čvorova u 1 bolesnika i supraklavikularnih limfnih čvorova u 2 bolesnika. Sve biopsije limfnih čvorova izvedene su kao ekscizijske biopsije. Malignitet je otkriven u 36 (49,3%) bolesnika, dok su u 37 (50,3%) bolesnika uzroci limfadenopatije bile dobroćudne patologije. Ispitivanje uzroka zloćudne bolesti pokazalo je da je limfom bio dijagnosticiran u 23 (31,5%) bolesnika. Hodgkinov limfom otkriven je u 5 bolesnika u kojih je dijagnosticiran limfom, dok je ne-Hodgkinov limfom utvrđen u 18 bolesnika. Metastatska limfadenopatija zabilježena je u 13 (17,8%) bolesnika. Među uzrocima dobroćudne limfadenopatije nađeni su reaktivna limfoidna hiperplazija (26%) i limfadenitis (20,5%). Broj izvađenih limfnih čvorova bio je od 1 do 4, a njihov promjer bio je od 9 do 75 (srednja vrijednost 29,53±15,56) mm. Nije bilo statistički značajne razlike između bolesnika s dobroćudnom i zloćudnom limfadenopatijom u dobi, spolu, promjeru limfnih čvorova, broju izvađenih limfnih čvorova i mjesta izvođenja ekscizijske biopsije limfnih čvorova. Za dijagnostičku biopsiju limfnih čvorova treba najprije napraviti tankoiglenu aspiracijsku biopsiju i širokoiglenu biopsiju. Ako se dijagnostički posumnja na limfom tada tankoiglena aspiracijska biopsija nije potrebna. U tom slučaju smatra se da je primjerenije najprije napraviti širokoiglenu biopsiju. Ako se širokoiglena biopsija pokaže nedostanom za postavljanje dijagnoze tada je primjerenije napraviti kiruršku biopsiju kako ne bi došlo do kašnjenja u dijagnozi i liječenju. Ekscizijska biopsija je metoda koja se može sigurno izvoditi i ne uzrokuje teži pobol kod palpabilnih perifernih limfadenopatija. Iako ne uzrokuje teži pobol s obzirom na to da je invazivni postupak, ekscizijsku biopsiju treba izvoditi u odabranoj skupini bolesnika.

Ključne riječi: *Limfadenopatija; Ekscizijska biopsija; Limfom; Reaktivna limfoidna hiperplazija; Limfadenitis*