Comparison of Referring and Final Pathology for Patients With Non-Hodgkin's Lymphoma in the National Comprehensive Cancer Network

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A B S T R A C T

Purpose

Before the implementation of the WHO lymphoma classification system, disagreement about pathologic diagnosis was common. We sought to estimate the impact of expert review in the modern era by comparing final pathologic diagnoses at five comprehensive cancer centers with diagnoses assigned at referring centers.

Patients and Methods

Patients in the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma (NHL) database with a documented pathologic diagnosis before presentation and a final pathologic diagnosis of any of five common B-cell NHLs were eligible. After central review of discordant cases, we estimated the rate of pathologic concordance, then investigated the etiology of discordance as well its potential impact on prognosis and treatment.

Results

The overall pathologic discordance rate was 6% (43 of 731 patients; 95% CI, 4% to 8%). For the majority of cases in which the referring diagnosis was apparently final, no additional studies were conducted at the NCCN center, and the change in diagnosis reflected a different interpretation of existing data. Concordance was highest for diffuse large B-cell lymphoma (95%) and follicular lymphoma (FL; grades 1, 2, and not otherwise specified, 95%) and lowest for grade 3 FL (88%). Of the 43 pathologically discordant cases, 81% (35 patients) might have experienced a change in treatment as a result of the pathologic reclassification.

Conclusion

In the era of the WHO lymphoma classification system, the majority of common B-cell NHLs diagnosed in the community were unchanged by second opinion review by an expert hematopathologist. However, for one patient in 20, there was a discordance in diagnosis that could have altered therapy.

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INTRODUCTION

The diagnosis of non-Hodgkin's lymphoma (NHL) has been a moving target, with multiple classification systems that have evolved significantly over the past several decades. The Rappaport system, developed in the 1950s, classified lymphomas based on morphologic appearance alone. In the 1970s, recognition that lymphomas are derived from B and T lymphocytes led to the development of the Lukes and Collins and the Kiel classification systems. The Working Formulation, introduced in 1982, was an attempt to group diseases based on clinical behavior and cell type. The Revised European American Lymphoma classification, published in 1994 and later refined to the cur-

rently used WHO classification, categorized specific disease entities based on a combination of morphologic, immunophenotypic, genetic, and clinical features.¹

Studies of concordance using earlier classification schema for NHL showed high levels of disagreement, even between expert hematopathologists.²⁻⁶ For example, pathologists from the Eastern Cooperative Oncology Group reviewed the institutional diagnosis of 670 cases through 1972 using the Rappaport Classification system. Although agreement was high (90%) in terms of histologic pattern (nodular *v* diffuse), the subtype and cell type were discordant in approximately one third of all cases.⁷ Adoption of the Working Formulation did little to improve diagnostic consistency.⁴

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With the development of the Revised European American Lymphoma classification system, which uses more reproducible methodologies (such as flow cytometry, immunoperoxidase staining, and cytogenetics), concordance between expert hematopathologists has improved. In the Non-Hodgkin's Lymphoma Classification Project, there was at least 85% agreement among expert hematopathologists using all available information (such as histology, immunophenotype, and clinical information). Immunophenotyping improved the diagnostic accuracy for 10% to 45% of all cases and was most important in mantle-cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and the T-cell lymphomas.²

There has not yet been a similarly comprehensive evaluation of the WHO classification schema. In a retrospective study published in abstract form, second opinion pathology review of NHL cases at a tertiary center in Toronto changed the diagnosis in 176 (16%) of 1,065 patients, most commonly from malignant to nonmalignant diagnoses (15.3%) and from more aggressive to less aggressive lymphoma subtypes (26.7%). Moreover, an independent physician panel determined that 16 patients with discordant pathology had been overtreated, four patients had been undertreated, two patients had been incorrectly treated, and nine patients had a significant change in planned treatment.⁸

Although the preliminary results of Kukreti's single-institution study are provocative, to our knowledge, there has not been a systematic multi-institution assessment of discordance rates for second opinion lymphoma pathology in the United States using the WHO classification schema. We sought to determine the rate of discordance for five common B-cell NHL diagnoses in five tertiary centers that participate in a large national lymphoma database. In addition, we determined whether additional information was obtained at the National Comprehensive Cancer Network (NCCN) center and estimated the likely impact of a change in diagnosis on treatment.

PATIENTS AND METHODS

The NCCN NHL Outcomes project is a multicenter prospective registry of comprehensive clinical, treatment, and outcome data for patients with NHL established on July 1, 2000. Five institutions contributed patients to this analysis: City of Hope Cancer Center, Duarte, CA; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; The University of Texas M. D. Anderson Cancer Center, Houston TX; and Roswell Park Cancer Institute, Buffalo, NY. The institutional review boards at all participating centers approved the data collection protocol for the NCCN NHL outcomes database. When required, we obtained written informed consent for medical record review.

All patients with newly diagnosed NHL (≤ 90 days from diagnostic biopsy date to first NCCN presentation) presenting to participating NCCN centers between July 1, 2000, and December 31, 2004, were eligible for inclusion. Additional inclusion criteria included documented pathologic diagnosis assessed at a referral center and final diagnosis of one of the following 10 final NHL WHO subtypes¹: follicular lymphoma (FL; grades 1, 2, 3 and not otherwise specified [NOS]), DLBCL, MCL, small lymphocytic lymphoma (SLL), nodal marginal zone lymphoma (NMZ), extranodal marginal zone lymphoma (EMZ), and splenic marginal zone lymphoma (SMZ).

We first compared the pathologic diagnosis from the referral center against the final WHO diagnosis at the NCCN centers to establish concordance rates, then we investigated the etiology of the discordance as well its potential impact on treatment. We defined pathologic concordance as the

same pathologic diagnosis at both the referring and NCCN center, considering all supporting documentation (pathology reports, immunohistochemistry and fluorescent in situ hybridization results, and physician progress notes 90 days before and after the date of initial positive biopsy for NHL). We considered all referral diagnoses of FL1, FL2, and FL NOS concordant if the final diagnosis was any of FL1, FL2, or FL NOS. Similarly, we considered all referral diagnoses of EMZ, NMZ, and SMZ concordant if the final diagnosis was any of EMZ, NMZ, or SMZ. Referral diagnoses of DLBCL and MCL were considered concordant only if the final diagnosis was DLBCL or MCL, respectively. Patients with two or more different histologies were classified according to the most aggressive histology. To ensure accuracy, we reviewed the referring diagnosis and final diagnosis of all nonconcordant treatment pairs in duplicate. First, central review of the records of all nonconcordant cases was performed by one of the authors, a medical oncologist specializing in lymphoma (A.S.L.). The study principal investigators (PIs) at the participating sites, all lymphoma specialists, reviewed all nonconcordant cases as well as a random 10% sample of concordant patients from their sites. The selection of the random cases was done centrally. We blinded the PIs to the results of the central review. Because the central reviewer was also a site investigator, we initiated this second review 2 months after the initial review to ensure sufficient wash-out time. We resolved disagreements by consensus between the central and site reviewers.

The site PIs were asked to assign each pathologically discordant case into one of the following categories: (1) referral diagnosis preliminary with further work-up suggested but not done before NCCN presentation; (2) referral diagnosis final, no additional studies at the NCCN center; (3) referral diagnosis final, additional biopsy done at the NCCN center; or (4) referral diagnosis final, additional studies other than biopsy performed at the NCCN center. To assess whether discordance would influence treatment, we classified diagnoses from the referring sites into seven categories: indolent (ie, FL 1, 2, or NOS, all types of marginal zone lymphoma (MZL) and SLL); FL 3; DLBCL; MCL; highly aggressive (ie, Burkitt's or lymphoblastic lymphoma); unspecified B-cell lymphoma; and other cancer. Because study eligibility was based on a qualifying NHL histology at the NCCN center, the NCCN treatment category list included only the first four of these classes. We defined treatment category concordance as the same treatment category at both the referral and NCCN center.

To assess the effect of the initial biopsy type, we calculated concordance according to the type of biopsy performed at the referring center (fine-needle aspirate [FNA], core biopsy, or other) and the biopsy site (nodal or extranodal). Patients who underwent both nodal and extranodal biopsy were classified as nodal. To assess the influence of ancillary testing, we calculated concordance on the basis of whether flow cytometry or immunohistochemical stains was performed before referral. We conducted separate χ^2 tests (or Fisher's exact test) using SAS version 9.1 (SAS Institute, Cary, NC) to determine whether there was a difference in concordance by biopsy type, diagnostic site, or if samples had ancillary testing.

RESULTS

There were 928 patients with newly diagnosed NHL presenting to a participating NCCN site between July 1, 2000, and December 31, 2004, in the database. Of these, 731 patients were referred from other centers, had a documented pathologic diagnosis before presentation at the NCCN, had a final diagnosis of one of the 10 NHL subtypes, and were thus eligible for inclusion in this analysis.

Review of the abstracted data identified 66 patients for whom the referring and NCCN assessed diagnoses were discordant. Of these, diagnoses for 42 patients were deemed truly discordant after central and site investigator review. One additional pathologically discordant case was identified among the sample of concordant cases reviewed and is included among the discordant cases for this

analysis. Overall, our pathologic discordance rate was 6% (95% CI, 4% to 8%; Table 1).

Pathologic concordance was highest for DLBCL, FL, and MZL. NCCN hematopathologists agreed with all 286 of the cases designated as DLBCL at the referring centers. However, 15 of the cases diagnosed as DLBCL at the NCCN center were assigned different diagnoses at the referring center, including FL (n = 6), Burkitt's lymphoma (n = 2), lymphoblastic lymphoma (n = 1), MCL (n = 1), MZL (n = 1), unspecified B-cell lymphoma (n = 1), and a diagnosis other than NHL (n = 3, Hodgkin's lymphoma, malignant thymoma, and anaplastic carcinoma). Of the 11 cases diagnosed as FL at the NCCN center, but assigned a different diagnosis at the referring center, eight cases had been classified using older classification schema or were called unspecified B-cell lymphomas; one was called SLL, one was called FL3, and one was called NMZ. The total number of cases diagnosed at the NCCN center as MZL, which included EMZ, NMZ, and SMZ, was small at 58 cases. Discordance occurred in only three cases; two were classified at the referral center as unspecified B-cell lymphoma, and one was classified as SLL. Seven cases of MCL had been assigned a different diagnosis at the referring center, including four cases called SLL. Conversely, three of 29 cases of SLL were discordant, two of which were initially called MCL.

The final diagnosis with the highest proportion of pathologic discordance (13%) was FL3, although the total number of cases was small (n = 32). Of the four discordant cases of FL3, two were called FL2, one was called FL1, and one was called FL NOS at the referring center.

Table 2 lists the basis of the change in pathologic diagnosis at the NCCN center. In four (9%) of the 43 cases, the pathologic diagnosis at the referring center was preliminary, with further evaluation recommended. For all other cases, the referring center pathology was apparently final. Most commonly, no additional studies were performed at the NCCN center (44%), and the change in diagnosis reflected a different interpretation of the existing data. In 21%, one or more additional biopsies were performed, and in 26%, other studies were performed, primarily immunoperoxidase stains. Fluorescent in situ hybridization cytogenetics was performed in one case.

The potential effect on treatment of pathologic discordance is presented in Table 3. Treatment category discordance occurred in 5% of cases overall (95% CI, 3% to 7%) and in 35 (81%) of the 43 patients for whom pathology was discordant. Two percent of patients with DLBCL were assigned a pathologic diagnosis at the referral center for which less aggressive therapy might be given, thus missing the opportunity for cure. In addition, all of the patients with FL3 who were pathologically discordant were also discordant with respect to treatment category, with the original diagnosis falling into the indolent category in all cases.

FNA and core biopsies accounted for 9% (n = 68) and 19% (n = 142) of initial biopsies at referral sites, respectively. There was no statistically significant difference in concordance between those who had FNA (94%; n = 64) or core biopsies (93%; n = 132) and those who had other biopsy types (94%, n = 492; *P* = .76). The

Table 1. Referral and Final Pathologic Diagnoses for Patients With Non-Hodgkin's Lymphoma (n = 731)

Referral Pathology	Final Pathology									
	FL NOS	FL1	FL	EMZ	NMZ	SMZ	SLL	FL3	DLBCL	MCL
FL NOS	5*	8*	3*	0	0	0	0	1	1	0
FL1	0	89*	7*	0	0	0	0	1	0	1
FL2	0	6*	88*	0	0	0	0	2	4	0
EMZ	0	0	0	36*	1*	0	0	0	0	0
NMZ	0	1	0	0	13*	1*	1	0	1	0
SMZ	0	0	0	0	0	4*	0	0	0	0
SLL	0	1	0	1	0	0	26*	0	0	4
FL3	0	0	1	0	0	0	0	28*	1	0
DLBCL	0	0	0	0	0	0	0	0	284*	0
MCL	0	0	0	0	0	0	2	0	1	89*
Unspecified B cell	0	2	1	1	0	0	0	0	1	1
Unspecified low-grade B cell	0	1	0	1	0	0	0	0	0	1
Diffuse mixed, small, and large cell	0	0	1	0	0	0	0	0	0	0
Diffuse small cleaved cell	0	1	0	0	0	0	0	0	0	0
Follicular, predominantly small cleaved cell	0	1	0	0	0	0	0	0	0	0
High-grade B-cell lymphoma, Burkitt's-like	0	0	0	0	0	0	0	0	2	0
Lymphoblastic	0	0	0	0	0	0	0	0	1	0
Nodular poorly differentiated lymphocytic	0	1	0	0	0	0	0	0	0	0
Other cancer	0	0	0	0	0	0	0	0	3	0
Total cases	5	111	101	39	14	5	29	32	299	96
Discordant cases										
%		5			5		10	12	5	7
No. of discordant cases		11			3		3	4	15	7
Total No. of cases evaluated		217			58		29	32	299	96

NOTE. The overall pathologic discordance rate was 6% (95% CI, 4% to 8%). Bold numbers represent discordant referral and final pathologic diagnoses.

Abbreviations: FL, follicular lymphoma; EMZ, extranodal marginal zone lymphoma; NMZ, nodal marginal zone lymphoma; SMZ, splenic marginal zone lymphoma; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle-cell lymphoma; NOS, not otherwise specified.

*Concordant referral and final pathologic diagnoses.

Table 2. Basis of the Change in Pathologic Diagnosis at the NCCN Center

Category	No.	%
Referral diagnosis preliminary with further workup suggested, but not done prior to NCCN presentation	4	9.3
Referral diagnosis final, no additional studies performed at the NCCN center	19	44.2
Referral diagnosis final, additional biopsy performed at the NCCN center	9	20.9
Referral diagnosis final, additional studies other than biopsy performed at the NCCN center	11	25.6
Total	43	

Abbreviation: NCCN, National Comprehensive Cancer Center.

proportions of nodal and extra-nodal referrals were 61% (n = 473) and 34% (n = 258), respectively. There was no statistically significant difference in concordance between nodal (94%; n = 443) and extranodal referral specimens (95%; n = 245; $P = .47$). Overall, 60% of cases (n = 437) had ancillary testing before presentation at the NCCN, with 28% (n = 120), 61% (n = 266), and 12% (n = 51) having flow cytometry, immunohistochemistry, or both tests, respectively. There was no statistically significant difference in concordance between referral specimens with (95%; n = 415) and without ancillary testing (93%; n = 273; $P = .24$).

DISCUSSION

At the five tertiary care institutions who participate in the NCCN NHL database project, agreement with the referring diagnoses for NHL was excellent at 94%. In addition, for DLBCL, the predominant subtype of NHL in adults, all cases diagnosed in the community were concordant. This finding implies that diagnoses rendered by community pathology departments, on the whole, are consistent with the subspecialized hematopathology at tertiary centers. It is important to note, however, that although the B-cell lymphomas included in this study represent approximately three quarters of all cases of lymphoma,⁹ they are arguably the most straightforward

lymphomas to diagnose. We excluded Hodgkin's, Burkitt's, lymphoblastic, and T-cell lymphomas, all of which may be more challenging and have been shown to have lower diagnostic reproducibility.² The fact that we found a much lower rate of discordance than the 16% reported in a recent Canadian study may reflect, at least in part, their inclusion of these rarer diagnoses. In addition, we considered all referral diagnoses of EMZ, NMZ, and SMZ concordant if the final diagnosis was any of EMZ, NMZ, or SMZ, given that these entities require clinical correlation. The adoption of the WHO classification system, with the inclusion of immunophenotyping and genetic tests, is probably the most important factor in the much higher rate of diagnostic accuracy and consistency we observed compared with that reported in older studies. Another possible explanation is that there is growing use of second opinion pathology review services performed by centers using expert hematopathologists who integrate state-of-the-art immunophenotyping and genetic testing into the diagnostic process.

Although this high rate of concordance is reassuring, the fact is that for 6% of patients, the diagnosis was changed by the NCCN center, and for 5% of patients, treatment also could have changed as a result. This raises several important policy questions. First, is it possible to identify a subset of patients who are at particular risk of misdiagnosis and to thus target tertiary care pathology review to patients most likely to benefit from it? And second, are there processes that could be routinely implemented in nontertiary care settings that would improve NHL diagnostic accuracy? Unfortunately, our results suggest that the answer to both questions is essentially no. Rates of discordance varied little across the five histologies we studied. And for the majority of cases with a final diagnosis from the referral center, no additional studies were performed at the NCCN center. Instead, the diagnosis was changed based on a review of the available material by an expert hematopathologist.

Our data also provide some insight into how routine review of NHL pathology at centers specializing in the diagnosis and care of this disease might affect patient outcomes. For 95% of patients with the most common NHL diagnoses, such review would not change treatment, and therefore, would not be expected to change outcomes. The patients most likely to benefit would be those for

Table 3. Referral and Final Treatment Category for Patients With Non-Hodgkin's Lymphoma (n = 731)

Referral Pathology Treatment Category	Final Pathology Treatment Category							
	Indolent* (n = 304)		FL3 (n = 32)		DLBCL (n = 299)		MCL (n = 96)	
	No.	%	No.	%	No.	%	No.	%
Indolent*	296†	97.0†	4	12.5	6	2.0	6	6.3
FL3	1	0.3	28†	87.5†	1	0.3	0	0
DLBCL	1	0.3	0	0	286†	95.0†	0	0
MCL	3	1.0	0	0	1	0.3	89†	92.7†
Highly aggressive‡	0	0	0	0	3	1.0	0	0
Unspecified B-cell lymphoma	4	1.3	0	0	1	0.3	1	1.0
Other cancer	0	0	0	0	3	1.0	0	0

NOTE. This table outlines the theoretical impact of histologic re-classification. Bold numbers represent discordant referral and final pathologic treatment categories. Abbreviations: FL3, grade 3 follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle-cell lymphoma.

*Includes grades 1 and 2 and "not otherwise specified" follicular lymphoma and extranodal marginal zone lymphoma, nodal marginal zone lymphoma, splenic marginal zone lymphoma, and small lymphocytic lymphoma.

†Concordant referral and final pathologic treatment categories.

‡Includes Burkitt's or lymphoblastic lymphoma.

whom review resulted in a change from an incurable diagnosis to a potentially curable one. Of 299 patients in our cohort with an NCCN center diagnosis of DLBCL, 15 patients were given discordant diagnoses at referral centers for which treatment might differ from the optimal therapy for DLBCL. Therefore, for 2% of all patients studied, pathology review was a potentially life-saving intervention. Review could also spare some patients unnecessary aggressive treatment. In our study, 3% of patients with an NCCN center diagnosis of indolent lymphoma (and 1% of patients overall) were assigned other diagnoses at the referring centers, diagnoses for which standard treatment might be different than for indolent lymphoma. There is an increasing tendency to treat indolent lymphoma with anthracycline-based chemotherapy; therefore, it is unlikely that treatment actually changed for all or even most of the patients for whom NCCN review resulted in a discordant treatment category. However, even for those who received the same treatment, what they were told about their prognosis was almost certainly affected. Finally, given that optimal therapy for FL3 and MCL have not been definitively established, it's difficult to estimate the likely impact on outcomes that would be expected for the 1% of our cohort with these entities who were discordant, assuming that the final NCCN diagnosis was accurate.

Our study has several limitations. First, because our study was conducted in tertiary care cancer centers, our population may have been enriched for particularly complex patients and the discordance rate therefore biased upward. However, the fact that our cohort was restricted to the five most common types of NHL likely diminished this kind of selection bias. Second, in estimating the potential impact of pathologic reclassification, we developed broad treatment-related categories representing general management approaches to NHL for both the referring and the ultimate diagnosis. The treatment of EMZ and SMZ may be distinct from other subtypes of indolent lymphoma. We did not examine the actual therapy received by patients for whom the pathologic diagnosis changed, because without information on the treatment that would have been given by the referring physician, it was not possible to determine whether therapy was changed as a result of the change in diagnosis. Finally, our case reviewers were all lymphoma oncologists, which could have introduced investigator bias. To guard against this, we conducted rigorous quality checks of our data, conducted in a blinded manner. Investigators reviewed all of the discordant cases from their institution as well as a random 10% of all concordant cases; we also blinded the reviewers at each institution to assessments by the PI.

In summary, using the NCCN lymphoma database, we found that in the era of the WHO lymphoma classification system, the majority of cases of the common B-cell NHLs diagnosed in the community were unchanged by second opinion review by an ex-

pert. For one patient in 20, however, there was a discordance in diagnosis that could have altered both prognosis and therapy. As newer molecular diagnostic techniques such as gene expression profiling are developed and impact both diagnosis and treatment, the reproducibility of this finding will need to be re-examined. The NCCN database will provide a comprehensive resource for this evaluation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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