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Centralized Review Offers Promise for the Clinician, the Pathologist, and the Patient With Newly Diagnosed Lymphoma

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Centralized pathology review of lymphoma diagnoses for clinical trials in the United States began in 1967 with the establishment of the Pathology Panel and Repository Center for Lymphoma Clinical Studies.¹ The concept emerged from discussions among DeVita, Rappaport, and Frei, and was organized under the auspices of the Lymphoma Task Force established by the National Cancer Institute in 1964.² The goal of the Task Force was to achieve a multidisciplinary and multi-institutional approach to the study of malignant lymphoma. It was recognized early on that accuracy and consistency in the diagnosis of lymphoma was essential for success of the clinical trials process, and that lymphoma diagnosis was a challenging area for most practicing pathologists. The Pathology Panel comprised a series of expert consultants who reviewed all protocol cases for the adult and pediatric cooperative groups.¹ After review by the expert panel, cases were reviewed secondarily at the Repository Center, and annual panel meetings were held to resolve any discrepancies. The review did not take place in real time, and therapy was generally initiated at the primary site before central review. However, central review did establish uniformity in diagnostic criteria for assessment of clinical trial results.

Since the 1960s, centralized pathology review for the diagnosis of lymphoma has been the accepted practice for clinical trials as well as for most large scale and comprehensive biologic studies, such as those undertaken by the Leukemia and Lymphoma Molecular Profiling Project of the National Cancer Institute³ or the Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe.⁴ The practice has ensured comparability of clinical trials and accurate comparison of genetic and genomic data among centers.

Centralized pathology review for the diagnosis of lymphoma has been largely restricted to the clinical research setting. However, practice patterns vary on an international basis, and in some countries, such as Germany, a significant proportion of routine cases are submitted for review. The report by Proctor et al⁵ in this issue of *Journal of Clinical Oncology* suggests that centralized pathology review has merit in the community setting and would contribute to improved patient care. The system instituted in North Central London is similar to that used by the All Wales Lymphoma Panel (AWLP).⁶ In both models, new lymphoma diagnoses were referred from regional general hospitals for review by the expert panel.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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However, there were some differences in approach. The AWLP reviewed cases without knowledge of the original diagnosis at the time of review. In contrast, the system adopted by the North Central London Lymphoma network (NCLLN) seems more collaborative and interactive. Ancillary studies performed at the primary institution were provided to the NCLLN pathologists, but the reference pathologists performed additional studies on an as-needed basis.

Discordance rates between the primary pathologist and the review diagnosis were roughly similar in the two studies: 17% for the AWLP and 27.3% for the NCLLN. These figures are substantially less than those reported in older studies, such as from the Pathology Panel for Lymphoma Clinical Studies, which reported agreement rates of only 51.6% for Hodgkin's lymphoma and 48.6% for non-Hodgkin's lymphoma.¹ The International Non-Hodgkin's Lymphoma Classification Project demonstrated that the detailed disease-defining approach used in the Revised European-American Lymphoma and WHO classifications, wherein diagnoses are determined on the basis of clearly delineated histologic, clinical, immunophenotypic, and molecular criteria, enhances reproducibility among experts.⁷ The study by Proctor et al⁵ confirms that this approach is transferable to the general community and seems to reduce discordant interpretations. Interestingly, the discordance rates decreased during the 6-year study, declining from 32% to 13%. The authors attribute this reduction to a gain in familiarity with the WHO classification by the general pathologists, as well as to the educational feedback sessions at which discordant cases were reviewed and discussed.

A more important figure is the number of cases in which a change in diagnosis resulted in a change in patient management. This occurred in a small but significant 2.1% of cases, including 22 cases in which there was discordance with respect to benign versus malignant diagnosis. Studies from the AWLP⁶ and the National Comprehensive Cancer Network⁸ found that in 8% and 4.9% of patients, discordant diagnoses would have influenced treatment decisions. Although these figures are small, a mistaken malignant or benign diagnosis is associated with major ramifications for the patient⁹ and significant medico-legal consequences for the physician.

Hospitals submitting cases to the NCLLN were charged a modest fixed fee of €180 (approximately \$220), which covered additional immunohistochemical or molecular testing using polymerase chain reaction. This figure is substantially less than the cost of outside consultation in the United States for cases submitted to a reference laboratory or expert consultant. Such costs usually run in the range of \$150 to \$200 for review of hematoxylin and eosin stained slides alone; fees for additional immunohistochemical studies are charged on a per-antibody-stain basis, usually in the range of \$125 to \$150 per stain. Molecular studies, including polymerase chain reaction analysis and fluorescent in situ hybridization, add substantial cost (\$350 to \$750), with the total fee for consultation that requires multidisciplinary testing easily reaching \$1,000 to \$1,500 or more. A significant difference in the two models is that in the NCLLN approach, all cases were submitted for review, which provided a steady source of funding for the laboratory effort, whereas in the United States, a community-based pathologist might submit only the most challenging or difficult cases for consultation.

One issue addressed by Proctor et al⁵ is whether all lymphoma cases should be directly referred to an expert hematopathologist, rather than handled by the two-step process used by the NCLLN. The authors argue for the latter approach, given that loss of exposure to this material by the general pathologist would result in a reduction in skill level and a deterioration of diagnostic ability with lymphoid lesions in general.

In conclusion, the system for expert central review implemented by the NCLLN offers significant advantages to the pathologist, the patient, and the clinical oncologist. The pathologist is provided with a ready means of obtaining expert opinion at a modest cost, and in turn, advances his or her knowledge in the field. The patient and clinician can proceed with the chosen therapeutic plan with confidence in the diagnosis. Central review has proven invaluable for the clinical trials process, and its introduction to routine clinical practice is a logical next step in improving patient care. Given the recent attention by the press to mistaken diagnoses in breast cancer,¹⁰ secondary review may be applicable to other tumor types as well. However, irrespective of the expertise of the pathologist or the number of reviewers, communication between the pathologist and the oncologist remains of paramount importance. An accurate diagnosis requires attention to clinical details, and a second look when the diagnosis does not fit. The pathologist and clinician must work together as a team and integrate clinical and pathologic data.

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