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Reproducibility and Prognostic Value of Different non-Hodgkin's Lymphoma Classifications: Study Based on the Clinicopathologic Relations Found in the EORTC Trial (20751)

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Abstract—*In the EORTC trial 20751, six pathologists belonging to five different centers classified tumoral lymph nodes from 406 untreated patients with non-Hodgkin's lymphoma (NHL) into three different NHL classifications. NHL were most easily and reliably subdivided according to the growth pattern (the rate of consensus being 93%). Classification according to growth pattern proved to be of prognostic significance. The rate of consensus of classifying cases in the different NHL classifications ranged from 74% for the Rappaport, through 70% for the Kiel to 67% for the international working formulation. It is concluded that NHL are reliably classified according to their growth pattern, and that this subdivision is of primary prognostic significance.*

INTRODUCTION

THE EORTC organized a non-Hodgkin's lymphoma (NHL) trial (EORTC trial 20751) during the years 1975-1980. Patients with nodal presentation in all stages of the disease were included. Lymphocytic lymphomas with a leukemic blood picture at the time of diagnosis as well as plasmacytomas were withdrawn from the trial. The treatment of the patients varied only according to the stage of the disease; the histologic subtype was not taken into account [1].

Several classifications on NHL have been reported, all of them being valuable and comparable in reproducibility and clinical relevance [2].

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Six pathologists, belonging to five different institutes, have retrospectively studied the biopsy material available from patients included in the trial. They classified all cases into the Rappaport classification [3], the Kiel classification [4] and the international working formulation [2]. The applicability of these classifications was assessed and their prognostic value and reproducibility evaluated.

MATERIALS AND METHODS

Haemotoxylin + eosin- and often PAS-, reticulin- and Giemsa-stained paraffin sections from tumoral lymph nodes obtained from 406 untreated patients were available for this study. The clinical staging procedures as well as the treatment procedures are reported elsewhere [1].

Six pathologists belonging to different institutes of pathology, situated in France, the Netherlands and Belgium, carried out the morphologic study.

All are experienced in lymph node pathology. Each pathologist classified each case into three different NHL classifications: the Rappaport classification, the Kiel classification and the international working formulation.

Only the results of those cases for which a consensus of at least 4 out of 6 pathologists was obtained were accepted for further analysis.

Overall survival has been used as the endpoint for the analysis of prognostic values. Survival curves have been estimated by the method of Kaplan and Meier [5]; the log-rank test [6] was used to compare survival between the different groups of patients.

RESULTS

From the 406 cases available for this morphologic study, 37 cases were omitted for various reasons: 12 cases were not accepted as NHL and 25 cases were excluded because of the poor quality of the available sections. Thus 369 remaining cases were available for subclassification into the Rappaport classification, the Kiel classification and the international working formulation.

Ninety-two percent of all cases should be evaluated for their growth pattern: 109 lymphomas demonstrated an easily recognisable nodular growth pattern; 182 lymphomas revealed a complete diffuse growth pattern; 50 cases were recognized as nodular and diffuse growing lymphomas. Survival data from 285 cases were available; these are shown in Fig. 1. The survival is significantly better for the nodular cases in comparison with the diffusely growing cases. Nodular and diffusely growing cases behave like nodular cases ($P = 0.1$). A further subclassification on the cell type in the Rappaport classification revealed 274 cases on which agreement was obtained.

Application of the Kiel classification revealed a consensus in 260 cases. Survival data from 216 cases were available. The survival data for the low- and high-grade malignant lymphomas are given in Fig. 2. In Fig. 3 the survival for the cases is illustrated analyzing them first for their growth pattern, next for their cell type.

Two hundred and forty-seven cases could be subclassified according to the international working formulation. Survival data from 212 cases were available. The survival curves for the low-, intermediate- and high-grade malignant lymphomas are given in Fig. 4. An unexpected survival curve is found for the small lymphocytic lymphomas with plasmacytoid features, all of them recognized as immunocytomas in the Kiel classification (Fig. 5).

DISCUSSION

From our results on 369 lymph nodes admitted to this study, consensus has been obtained most easily by subdividing NHL according to the growth pattern of the tumor (Table 1). Even without any prior discussion on criteria to be used to categorize NHL into nodular-, nodular and

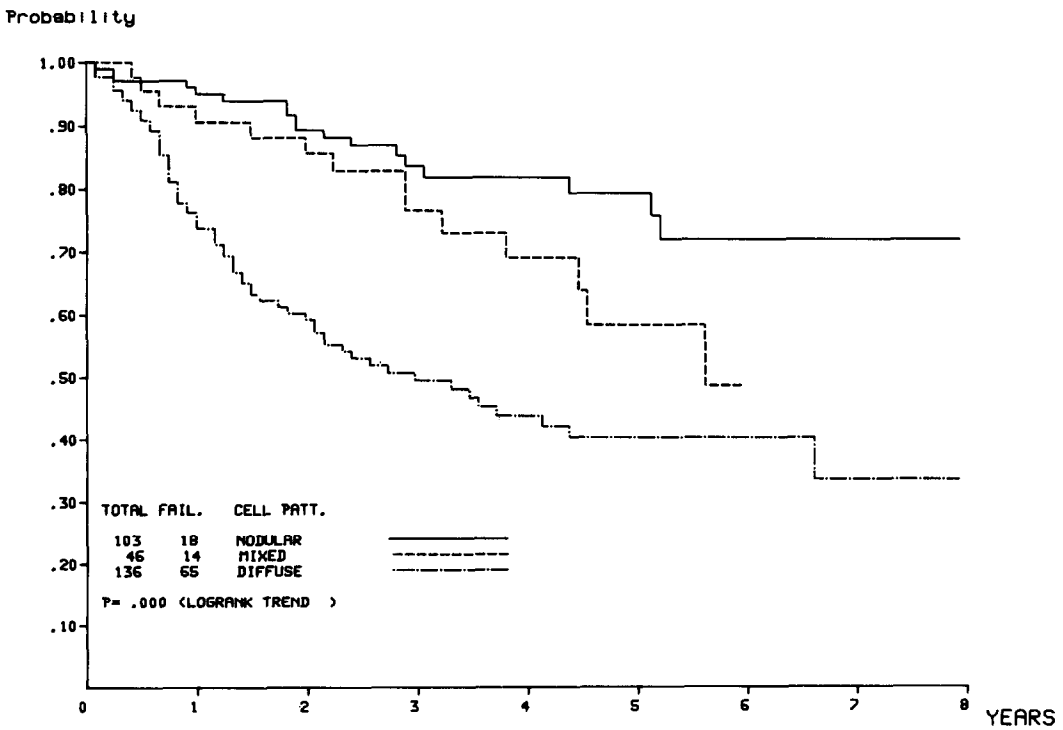

Fig. 1. Survival in years for NHL according to growth pattern.

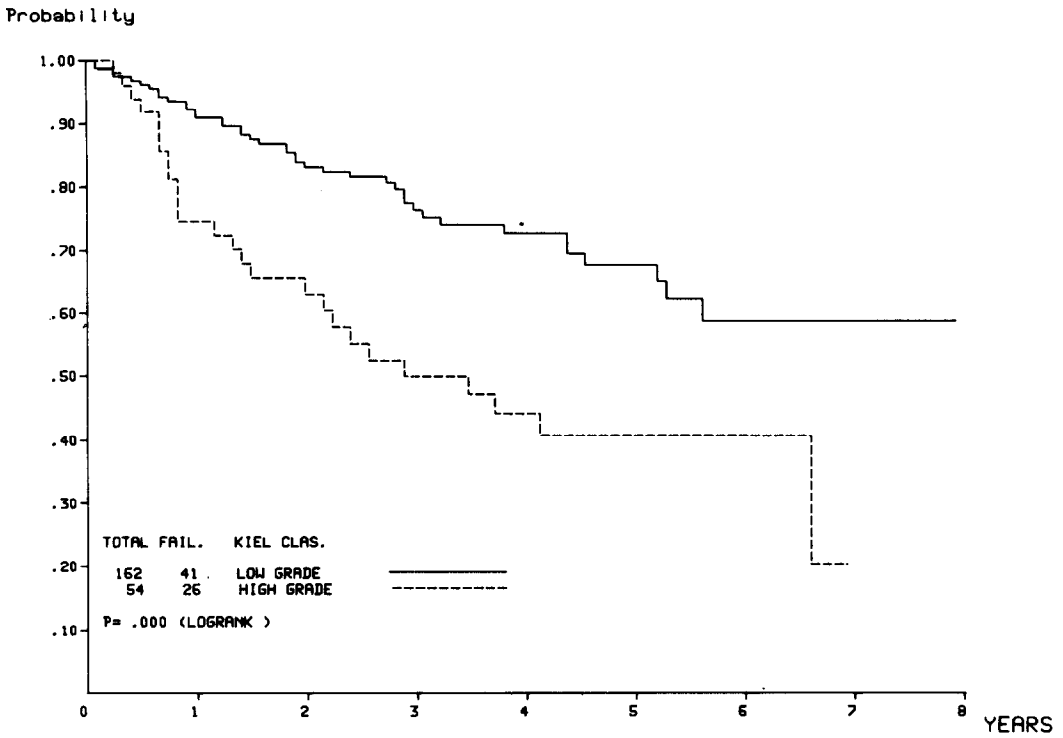

Fig. 2. Survival in years for NHL according to the Kiel classification.

diffuse- and diffusely growing groups, agreement was obtained in 93% of all cases. Moreover, this subdivision turns out to be of prognostic significance as illustrated in Fig. 1.

Both the nodular- and the nodular and diffuse lymphomas do have a statistically significant difference in prognosis in comparison with the diffuse lymphomas. These data underline the clinical usefulness of subdividing NHL on their growth pattern as previously reported [2,7].

The degree of nodularity has not been evaluated by a grading system in our study. In contrast with

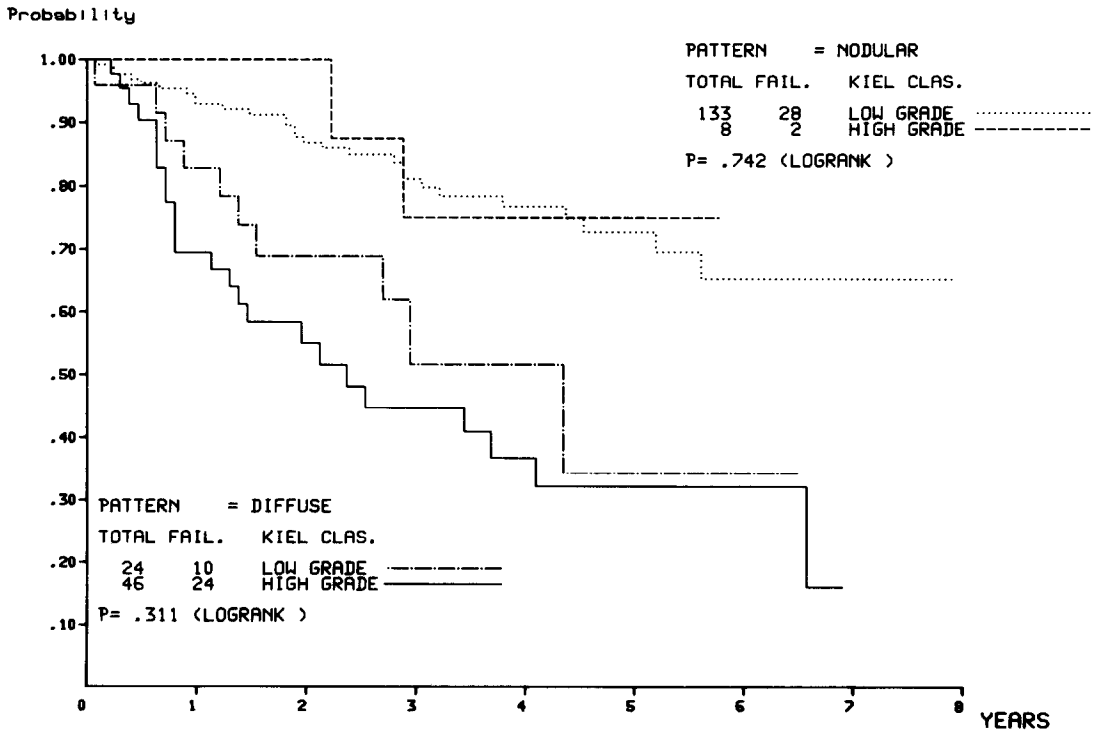

Fig. 3. Survival in years for NHL analyzing them first for their growth pattern, next for their cell type.

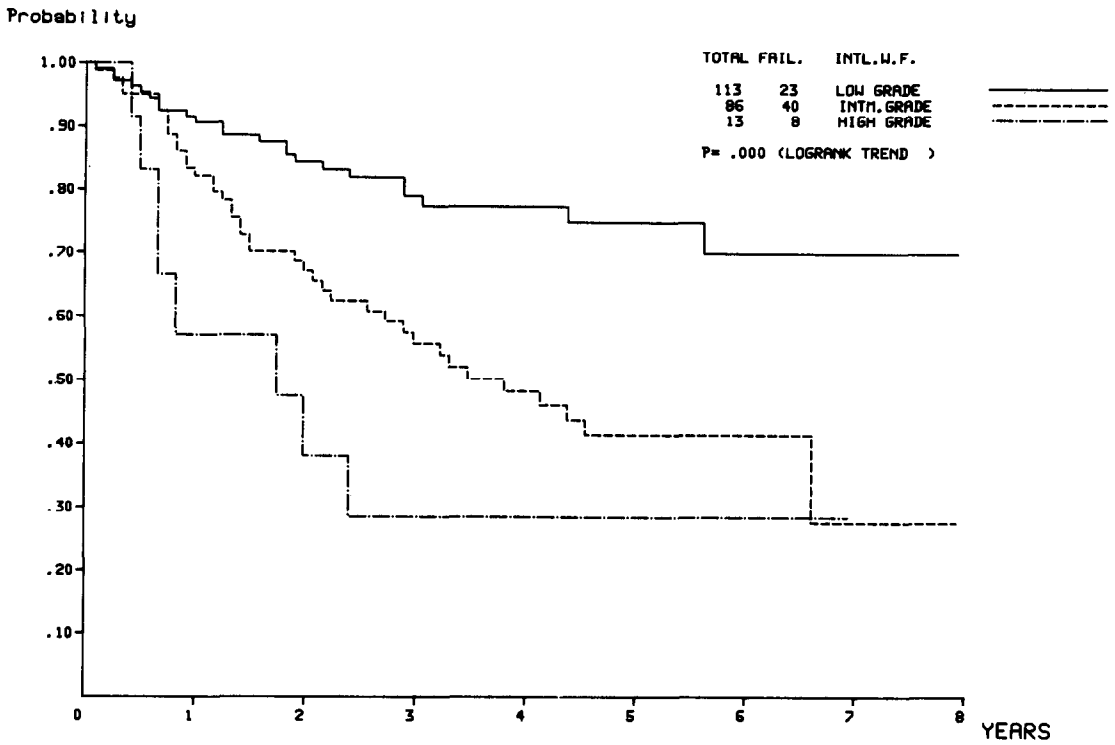

Fig. 4. Survival in years for NHL according to the international working formulation.

previous studies, which claim the importance of the degree in nodularity [8], but in accordance with other studies [2], we did not find a statistical difference in prognosis between the nodular- and the nodular and diffuse lymphomas.

As both survival curves ran closely together, both groups have been put together for the rest of the study.

Lennert *et al.* [9] have stated that the growth pattern of lymphomas is related to their

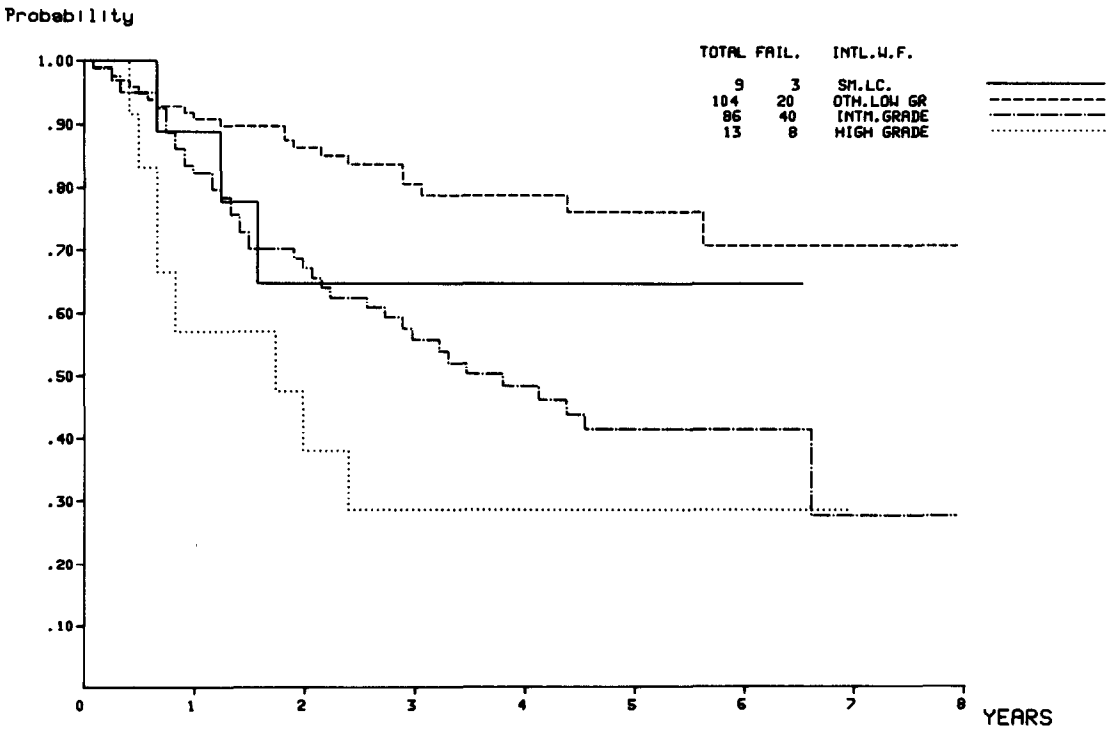

Fig. 5. Survival in years for NHL according to the international working formulation with a separate curve for the small lymphocytic lymphomas with plasmacytoid features.

proliferating cell type, thus stressing the need for a subdivision of NHL on the basis of the cell type. Such subtyping revealed less agreement in our pathology panel, irrespective of the classification applied (Table 2). However, the rate of consensus we obtained is comparable to previously reported results [2].

In the Kiel classification a consensus was obtained in 70% of all cases. Apparently subtyping according to the Kiel classification seems to be reliable for lymphomas with a nodular growth pattern (Table 3) as an agreement was obtained for practically all nodular cases. However, only in 55% of the diffuse cases was consensus reached in the Kiel classification according to the cell type.

As suggested by Lennert *et al.* [10] and as illustrated since by several clinicopathological studies [11], the survival of lymphomas recognized as low-grade malignant is indeed statistically different from those recognized as high-grade malignant (Fig. 2). Although this difference in behaviour might suggest an analogy with the difference in prognosis found by subtyping lymphomas according to their growth pattern, it has to be realized that the comparable groups are composed of partly different cases.

Therefore we performed a stratification by growth pattern, followed by a stratification by cell type according to the Kiel classification and vice versa (Fig. 3). From Fig. 3 we can conclude that, once subgrouping of NHL according to growth pattern has been performed, further subdivision of cell types reveals no significant prognostic value; nodular groups as well as diffuse groups present survival curves close to each other, as indicated by the *P* values. Similar findings have been reported previously [12, 13]. The comparison in the diffuse lymphomas might have been better assessed if agreement on the cell type had also been reached in the 81 cases recognized as diffuse growing lymphomas but not further classified on their cell type.

Most cases with a nodular growth pattern were composed of germinal centre cells, the majority exhibiting a mixture of centroblasts and centrocytes. Concerning survival, this type of lymphoma has to be distinguished from the other NHL; moreover, this type of lymphoma is easily recognized with a high reproducibility.

In the international working formulation, agreement was obtained in 67% of all cases. These cases can be subgraded into three groups (Fig. 4).

The small lymphocytic lymphomas from this study are represented by lymphocytic lymphomas with plasmacytoid features (chronic lymphocytic leukemia was omitted from the trial). These lymphomas do not behave similar to the remaining lymphomas of low-grade malignancy on one hand, and on the other hand show no difference in prognosis from the intermediate- and high-grade malignant categories (Fig. 5). Although the number of patients is low, this unexpected survival curve supports the validity of recognizing lymphocytic lymphomas with plasmacytoid features, or immunocytomas, as a separate entity.

Finally, one can speculate about the reasons for having no agreement in 45% of the diffuse NHL when subclassifying them according to their cell type. Firstly, it is clear that nodular lymphomas represent a homogeneous group of tumours composed of germinal center cells. One can even speculate that the nodular architecture might have biased the pathologists to identify the tumoral cells as germinal center cells. In contrast, diffusely growing NHL represent a heterogen-

Table 1. Rate of consensus for the growth pattern

341 cases were classified for the growth pattern	(93% of all cases)
109 cases with a nodular growth pattern	
50 cases with a mixed growth pattern	
182 cases with a diffuse growth pattern	

Table 2. Rate of consensus in the different NHL classifications

274 cases for the Rappaport classification	(74% of all cases)
260 cases for the Kiel classification	(70% of all cases)
247 cases for the international working formulation	(67% of all cases)

Table 3. Rate of consensus in the Kiel classification according to growth pattern

108 cases amongst 109 cases with a nodular growth pattern
42 cases amongst 50 cases with a nodular and diffuse growth pattern
101 cases amongst 182 cases with a diffuse growth pattern

eous group of lymphomas with a pronounced variability in their proliferating tumor cells. Secondly, the cases available for this study have been collected from 22 clinical centers; neither the applied preparation techniques nor the technical quality of the available sections were standardized. Thirdly, this study was carried out by six pathologists belonging to different centers. Only those results for which a consensus was obtained in four out of the six panel members were accepted for statistical analysis.

Therefore the finding that non-Hodgkin's lymphomas are subdivided most easily and most reliably according to their growth pattern, and that this subdivision is of primary prognostic value, has to be related with the above given remarks on the present conditions of the study.

REFERENCES

1. Burgers JMV, Somers R, Quasim MM, Van Glabbeke M. Report on the EORTC lymphoma trial 20751. *Int J Radiat Oncol Biol Phys* 1983, **9**, 11-15.
2. National Cancer Institute sponsored study of classifications of non Hodgkin's Lymphomas. *Cancer* 1982, **49**, 2112-2121.
3. Rappaport H. Tumors of the hematopoietic system. *Atlas of Tumor Pathology*, Section 3, Fasc. 8. Washington, DC, Armed Forces Institute of Pathology, 1966.
4. Lennert K, Mohri N, Stein H, Kaiserling E. The histopathology of malignant lymphoma. *Br J Haematol (Suppl)* 1975, **31**, 193-203.
5. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. *JAMA* 1958, **53**, 457-481.
6. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163-170.
7. Anderson T, De Vita VT, Simon RM *et al.* Malignant lymphomas. II Prognostic factors and response to treatment of 473 patients at the National Cancer Institute. *Cancer* 1982, **50**, 2708-2721.
8. Dambler L, Lenner P, Lundgren E. The impact of growth pattern on survival in non-Hodgkin's lymphomas classified according to Lukes and Collins. *Pathol Res Pract* 1982, **174**, 42-52.
9. Lennert K, Collins RD, Lukes RJ. Concordance of the Keil and Lukes-Collins classifications of non-Hodgkin's lymphomas. *Histopathology* 1983, **7**, 549-559.
10. Lennert K, Mohri N, Stein H, Kaiserling E, Muller-Hermelink HK. *Malignant Lymphomas Other than Hodgkin's Disease.* Berlin, Springer Verlag, 1978, 101-106.
11. Brittinger G, Schmalhorst U, Bartels H *et al.* Principles and present status of a prospective multicenter study on the clinical relevance of the Kiel classification. *Blut* 1981, **43**, 155-166.
12. Lenner P, Lundgren E, Dambler L. Clinico-pathologic correlation in non-Hodgkin's lymphomas II. Clinical and prognostic significance of nodularity. *Acta Radiol Oncol* 1979, **18**, 417-430.
13. Grimelius B, Sundstrom C. Morphologic classification of non-Hodgkin's lymphomas. *Acta Radiol Oncol* 1982, **21**, 289-297.