rectly differentiated. Finally, our preliminary results also point towards trephine as the most informative and occasionally unique material for identifying certain particular lymphoma entities.

Conclusion

Histological examination of the bone marrow based on an evaluation of trephine biopsies is the gold standard for the diagnosis of bone marrow involvement in non-Hodgkin's lymphomas while immunohistochemistry and molecular analysis may increase the accuracy and the sensitivity of lymphoma detection. Subtyping lymphomas on the trephine, according to the REAL classification, needs further investigation.

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Philadelphia chromosome-negative (Ph1-) chronic myeloproliferative disorders. A synoptic approach

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Progress in the understanding and definition of the three main subtypes of Ph1- chronic myeloproliferative disorders (CMPDs), idiopathic (primary) myelofibrosis (IMF), polycythemia vera (PV) and essential thrombocythemia (ET) seems to be most promising when pursuing a synoptic approach to this problem. This implies not only close cooperation With the clinicians and reference to hematological data (1) but also a clear-cut distinction between reactive lesions *(i.e.,* spurious polycythemias *vs.* PV or thrombocytosis *vs.* ET) in the initial stages of the disease process (2, 3). Considerable difficulties may arise in distinguishing thrombocythemias (4) and (osteo)-myelofibrosis (5), which eventually occur in all three subtypes of Ph1- CMPDs (4, 6). In addition to semiquantitative staging systems (Hannover Classification), which are based on histological features in pretreatment (6) and sequential bone marrow biopsies (5, 7), more elaborate teChniques such as histochemistry and morphometry are warranted (Table 1). In this context controversy still persists regarding morphological criteria (8), in particular megakaryopoiesis as one of the most distinctive hallmarks of histopathology (4-7). Moreover, a difference of opinion has been expressed concerning the so-called prefibrotic initial stages of IMF. This implicates predominantly their stage-like evolution into myelofibrosis (4, 5, 7), presenting clinical features and diagnostic criteria (9-11) and, when accompanied by an elevated platelet count, also their differentiation from ET (Table 2). Altogether, laboratory data and morphological variables should be considered equally to construct corresponding risk groups which are essential for the design of clinical trials aiming to improve treatment strategies (10,12). The determination of features indicating prognosis have to include parameters Characterizing dynamics of hematopoietic cell kinetics (13), such as proliferating cell nuclear antigen (PCNA), Ki-S1 (topoisomerase-II alpha) and apoptosis. The rationale of this procedure is to obtain a deeper insight into leukemic cell turnover (14) and to significantly

Table 1. Morphometric characteristics (mean ±SD) at diagnosis of patients regarding several bone marrow features in Ph1-chronic myeloproliferative disorders compared with a control group.

	Normal bone marrow	Polycythemia vera	Idiopathic myelofibrosis	Essential thrombocythemia
Number of patients	20	115	150	40
Cellularity (%)	50.5±13.9	88.1±7.9	81.9±12.4	70.8±6.6
Erythropoiesis x10^2/mm^2 (Ret 40 f)	14.6±2.7	36.9±6.7	7.2±3.8	16.1±3.0
Granulopoiesis x10^2/mm^2 (naphthol-AS-D-chloroacetate esterase reaction)	39.0±6.3	58.7±8.8	40.1±25.0	37.4±6.3
Megakaryopoiesis/mm^2 (0061)	24.4±5.3 (14.0-30.1)	102.6±24.2 (52.1-145.2)	79.9±29.9 (36.8-184.0)	126.6±35.6 (66.5-197.2)
Macrophages x10^2/mm^2 (0068)	3.0±1.2	3.9±1.2	7.4±1.3	3.7±0.7
Fibers x10^2/mm^2 (Gomori's stain)	16.1±5.1 (4.1-19.5)	21.6±10.3 (5.4-38.6)	93.5±32.8 (16.1-160.3)	14.9±6.1 (6.6-30.5)
Fraction with myelofibrosis (%)	0	17	84	0

Because of the wide ranges, corresponding values (in brackets) are given for megakaryocytes and fibers. The incidence of (reticulir - collagen) myelofibrosis for all entities (cut-off point, doubling of normal reticulin stain, measured fiber density) la also indicated.

Table 2. The Cologne Criteria (4) for the diagnosis and staging of idiopathic myelofibrosis (IMF).

A	No preceding or allied other subtype of myeloproliferative disorders or myelodysplastic syndromes
B	Splenomegaly (or palpation or >11 cm ultrasound)
C	Thrombocythemia (platelet count >500 x 110^9/l)
D	Anemia (Hb <12 g/dl)
E	Definitive leukoerythroblastic blood picture
F	Histopathology: granulocytic plus megakaryocytic myeloproliferation with large, multilobulated nuclei containing megakaryocytes which show abnormal clustering and definitive naturation defects and the following: i) no to minimal reticulin fibrosis; ii) slight reticulin fibrosis; ii) marked increase (density) in reticulin fibers or collagen fibrosis; iv) osteosclerosis (endophytic bone formation).

Diagnosis and classification of IMF is acceptable if the following combinations are present:

Stage 1:	A+B+C+F1 is consistent with a hypercellular (prefibrotic) stage simulating clinically essential thrombodythemia
Stage 2:	A+B+C+D+F2 la consistent with early IMF
Stage 3:	A+B+D+F3 is consistent with manifest IMF
Stage 4:	A+B+D+E+F3+4 is consistent with advanced IMF complicated by osteosclerosis (osteomyelosclerosis)

Table 3. Simplified synthesis prognostic staging system (Cologne score) in idiopathic (primary) myelofibrosis (IMF) derived from a clinicopathological study on 120 patients (13).

Parameter		Prognostic impact (score)
Age (years)	>70	2
Hb (g/dl)	<10	2
Thrombocytes (x10^9/l)	<300	I
Leukocytes (x10^9A)	>20	1
Myaloblasts (%)	>2	
Erythroblasts (%)	>2	
Proliferating cell nuclear antigen index (per mm3)	<240	0.5
Apoptosis (per mm3)	<6	0.5

		Survival		
Prognostic staging Risk group	Score (points)	Observed (months)	Relative (5 years)	Proportion of life loss
Low risk	<2	157	78%	14.98%
Intermediate risk	>2 and <4	45	42%	60.23%
High risk	>4	15	10%	76.71%

improve the impact of risk profiles (Table 3). Thus a substantial advance in diagnostic and prognostic efficiency may be achieved by a concerted action involving a refined histological evaluation and a close consideration of clinical findings.

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Chronic myelogenous leukemia. An update

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Chronic myelogenous leukemia (CML) comprises four groups that are under discussion at present. These are: i) Philadelphia (Ph)-positive, BCR-positive CML; ii) Ph-negative, BOR-positive CML; ii) atypical CML (aCML), *i.e.* Ph-negative, BOR-negative aCML; and iv) chronic myelomonocytic leukemia (CMML), which actually belongs into the myelodysplastic syndromes but which must be discussed in this context. The first group is by far the largest, with over 90% occurrence among all CMLs. The second group is believed to form about 4% (1). CMML is presumed to have approximately 3% frequency and the new category of aCML is even more rarely observed (2-4). Neutrophil leukemias are seldom detected and are thus not considered within this article. Recent results of bone marrow pathology focus on the large group of Ph-positive CML and on pH-negative, BCR-positive CML since patients of the second group have similar clinical characteristics and outcome (1, 2, 5). Patients of both groups benefit from protocol therapy with interferon-a (IFN-a) or hydroxyurea, which has prolonged their mean life expectancy from 3-4 years to about 5 years overall survival (5, 6).