SUMMARY
POSTGRADUATE STUDY IN CLINICAL CYTOLOGY SINCE 1967 — FOUNDATION AND IMPACT ON THE DEVELOPMENT OF CYTOLOGY IN CROATIA
I. ČREPINKO, I. KARDUM–SKELIN1, V. MAHOVLIĆ2 and K. KUDRNA–PRAŠEK3
Academy of Medical Sciences of Croatia and Croatian Society of Clinical Cytology, Croatian Medical Association, Zagreb;
1Merkur University Hospital; 2Zagreb University Hospital Center, Zagreb and 3School of Medicine, University of Zagreb, Zagreb, Croatia
In Croatia, clinicians were the first to introduce clinical cytology in the first half of the 20th century. At that time, Beata Brauzil introduced morphological diagnosis in hematology and educated a critical number of clinicians and other enthusiasts interested in cytology. Following the 1963 World Health Organization guidelines on the value of cytodiagnosis in the early detection of cancer and the need of respective education in cytology of medical students, clinicians, pathologists and other professionals, Erik Hauptmann, an internist (as the first head) and Ante Zimolo, a pathologist, initiated foundation of the Postgraduate Study in Medical/Clinical Cytology (PSMCC) in 1967. The study curriculum has since been revised twice, i.e. in 1996 with the introduction of professional studies and in 2005 as a specialist study. During the 40 years of its existence, 31 postgraduate studies have been organized, with 407 students enrolled, 380 students that completed the study and 119 students having acquired the MS degree. The efforts invested by the PSMCC students and lecturers contributed to the development of clinical cytology. The Section of Cytology and Cytodiagnosis (now Croatian Society of Clinical Cytology) of the Croatian Medical Association was founded in 1970. However, the good theoretical basis provided by PSMCC but inadequate practical work pointed to the need of the respective residency, founded in 1974. Then, PSMCC became an integral part of residency in clinical cytology. In the scope of the Croatia’s pursuit of EU membership, the Task Force for Cytology of the Ministry of Health and Social Welfare of the Republic of Croatia has prepared the Residency Curriculum Proposal within the frame of clinical morphology professions with a common basis and directed towards cytopathology. In 1968, only one year of the PSMCC foundation, Inga Črepinko organized the first form of additional training for cytotechnicians. Accordingly, the foundation of PSMCC had driven a number of factors that have resulted in 48 units of clinical cytology currently active in 21 Croatian towns, employing 128 clinical cytologists, 13 other specialists and 122 cytotechnologists.

Key words: postgraduate study, clinical cytology, development of cytology in Croatia

SUMMARY
SINGLE CELL — DEFINITIVE DIAGNOSIS!
WHERE THE PROFESSION ENDS AND THE ART BEGINS?
Merkur University Hospital, 1Zagreb University Hospital Center, 2Dubrava University Hospital, Zagreb,
3Rijeka University Hospital Center, Rijeka, Croatia
Cell is a morphologically and functionally the tiniest living organism, present from the very beginning of life on the Earth. Specialized cell types make up specific tissues and organs of the human body. Cell itself and cell elements are liable to morphological, functional,
phenotypic and genotypic alterations in various physiological and pathological states. These alterations are studied by cytodiagnosis to diagnose the disease at cellular level. Cytologic examinations belong to the group of morphological, non–aggressive or minimally invasive tests that are easy to perform for both the patient and the professional. In addition, these tests are highly reliable and preferred to the related diagnostic procedures for providing immediate orientation and definitive diagnosis, thus saving both time and money. With the introduction of adjunctive technologies such as cell–surface marker analysis, computer image analysis, molecular and cytogenetic technologies performed on cytologic smears, cytology has become an even more important factor in the diagnosis, subtyping and prognosis of malignant tumors. Thorough knowledge of cell morphology is a basis for proper performance and understanding of cytology techniques. A cytologist needs to be familiar with clinical manifestations of the disease and to be informed on all relevant data on the patient and his current and previous medical history, in order to be able to issue findings that are understandable and usable to all clinicians and patients. It requires close collaboration between the cytology laboratory and the ward, and among the cytologist, the patient and the clinician. Good collaboration with other diagnostic professions such as pathology, laboratory, molecular and cytogenetic diagnosis is by no means less important. Cytology as a profession implies knowledge of the morphological characteristics of normal cells and cells in various physiologic states, along with due knowledge of the morphology, phenotypic and genetic features of pathologic alterations. However, synchronizing and combining cytologic morphology with other sophisticated diagnostic procedures to reach an accurate diagnosis, subtyping and prognosis of tumor disease is artistry indeed.

Key words: cytology, cytochemistry, immunocytochemistry, cytogenetics and molecular diagnosis, computer image analysis

SUMMARY
CLINICAL AND LABORATORY PROGNOSTIC PARAMETERS FOR LEUKEMIC TYPES OF CHRONIC LYMPHOPROLIFERATIVE DISEASES
I. KARDUM–SKELIN, A. PLANINC–PERAICA, S. OSTOJIĆ KOLONIĆ, H. MINIGO, D. RADIĆ–KRIŠTO,
D. ŠUŠTERČIĆ, M. MILAS, R. VRHOVAC and B. JAKŠIĆ
Merkur University Hospital, Zagreb, Croatia
Aim: The aim of the study was to identify the clinical and laboratory (hematologic, biochemical and morphological) prognostic parameters of chronic leukemic lymphoproliferative diseases (CLLPD).
Methods: The study included 155 CLLPD patients. Analysis was performed in the overall CLLPD population and separately in a subgroup of patients with B chronic lymphocytic leukemia with variants (B–CLL+V) including typical B chronic lymphocytic leukemia (B–CLL), mixed chronic lymphocytic leukemia and prolymphocytic leukemia (CLL/PLL), and a variant of chronic lymphocytic leukemia with lymphoplasmocytoid differentiation (CLL/IMC). Kaplan–Meier method (Statistica 7.1) was used on survival analysis.
Results: Male patients older than 62 (p=0.03991), female patients (p=0.02871), patients not receiving antitumor therapy on study entry (p=0.01902) and patients not treated for CLLPB upon study entry (p=0.04076) showed better survival rate. Older patients predominated in the group requiring no antitumor therapy (p=0.019247). Analysis of sex distribution yielded an equal male to female ratio in the overall CLLPD population and B–CLL+V subgroup. Mann–
Whitney U–test was used to assess the clinical significance of quantitative parameters related to patient age and sex. The level of bilirubin, the size of cervical lymph nodes and doubling of peripheral blood lymphocytosis (DTL) were lower in the group of older patients (>60 years). Men had higher levels of hemoglobin, bilirubin, SGOT and creatinine, and larger spleen and liver. Statistically significant survival differences were recorded for 16 of 20 clinical parameters. Patients older than 60, female patients and patients receiving no antitumor therapy showed better survival. Lower clinical stage according to Rai and Binet and total tumor mass (TTM) lower than 9 indicated better prognosis, whereas patients with spleen enlargement and multiple regions involved with lymph node enlargement showed poorer survival. B–CLL+V patients and patients free from doubling of total tumor (DTM) or of absolute lymphocyte count (DTL) within 12 months had better survival than the overall CLLPD patient population. A statistically significant survival difference was recorded for 5 of 15 bone marrow (BM) parameters tested: normal and less cellular BM puncture specimen, >70% of all lymphatic cells, >16% of atypical lymphatic cells, and >18% of granulocytes in myelogram indicated better prognosis. Poorer disease outcome was associated with interstitial and nodular infiltration found on bone biopsy. Ten of 20 hematologic parameters were found to be statistically significant. Poorer prognosis was associated with red blood cell count <2.5x1012/L, leukocyte count >100x109/L, reticulocyte count >5/103 E, hemoglobin <100 g/L and iron <15 mol/L. Better survival was associated with absolute count of total lymphatic cells <100x109/L and absolute count of atypical lymphatic cells <5x109/L in peripheral blood; <10% of all atypical lymphatic cells, >5.1% monocytes and >10.1% granulocytes in differential blood count. Statistically significant survival differences were found for 10 of 20 biochemical parameters tested. Poorer survival was recorded in patients with LDH >300 U/L, SGOT >24 U/L, calcium <2.3 mmol/L, total protein <66.1 g/L, albumin <40 g/L, a2 globulin <5.9 g/L, b globulin <7.3 g/L, g globulin <9 g/L and IgG <10 g/L. Better prognosis was only indicated by lower levels of IgM (<0.91 g/L). Conclusion: Careful clinical examination is an important step on assessing the extent and progression of the disease, and a major chain on tailoring individualized therapeutic approach, along with clinical stages according to Rai and Binet, CLLPD subtype and progression factors (DTM and DTL). Laboratory parameters (hematologic and biochemical) as objective quantitative parameters obtained by simple venipuncture, in contrast to the ’researcher–dependent’ ones, increase the utilization of some of these parameters as risk factors in CLL.

Key words: chronic leukemic lymphoproliferative disorders, chronic lymphocytic leukemia, clinical and laboratory prognostic parameters

SUMMARY
CYTOMORPHOLOGICAL CHARACTERISTICS OF THYROID PAPILLARY CARCINOMA
AND THEIR PROGNOSTIC VALUE
A. KNEŽEVIĆ–OBAD and I. KNEŽEVIĆ–ŠTROMAR
University Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Center and I Sunce Polyclinic, Zagreb, Croatia
Objective: The aim of this study was to determine cytomorphological characteristics of classic papillary carcinoma that could point to a higher likelihood of intraglandular or paraglandular dissemination of the disease.
Methods: Morphological characteristics of classic thyroid papillary carcinoma and the size and ultrasonography characteristics of thyroid nodules were semiquantitatively analyzed in
100 patients diagnosed with papillary carcinoma by cytology and verified by histology. Data on the presence of intraglandular and paraglandular dissemination, established by histologic examination of postoperative material, were collected and analyzed.

Results: There were 16 male and 84 female patients aged 4–78 (mean 48.8) years. Polymorphism, multinucleation, intranuclear inclusions, psammoma bodies, presence of follicles, Hürthle like cells and connective tissue elements were present in 31%, 62%, 88%, 19%, 16%, 26%, 10% of cases, respectively. Thyroid nodule size was 4–80 mm (mean 14.5 mm) and up to 10 mm in 50% of cases; 76% of nodules were hypoechoic, 96% had irregular margins, and calcifications were present in 71% of nodules. Intraglandular dissemination and neck lymph node metastases were found in 16% of patients. Paraglandular dissemination was observed in 15% of cases. Statistical analysis showed no significant cytologic characteristic that would imply a higher or lower likelihood of intraglandular dissemination. Older age was found to be a risk factor for paraglandular but not intraglandular dissemination, while nodule size and neck lymph node metastases were not important for the presence of intraglandular or paraglandular dissemination.

Conclusion: Since no marker that could indicate a higher or lower likelihood of intraglandular and/or paraglandular dissemination of thyroid papillary carcinoma has yet been identified, it is advisable to perform total thyroidectomy when papillary carcinoma is diagnosed by cytologic examination, irrespective of the nodule size or tumor subtype.

Key words: thyroid carcinoma, thyroid nodule, papillary carcinoma, cytopathology, ultrasonography

SUMMARY
THYROID TRANSCRIPTION FACTOR–1 IN PULMONARY CYTOLOGY
S. SMOJVER–JEŽEK, B. VRABEC–BRANICA, Z. JUROŠ, Z. BORAS1, B. ĆUČEVIĆ1 and I. MAŽURANIĆ2
Departments of Cytology, 1Pneumology and 2Radiology, Jordanovac University Hospital for Lung Diseases, Zagreb, Croatia

Currently it is necessary to define in almost each case whether a carcinoma is a small or non–small cell carcinoma, adenocarcinoma, pulmonary or metastatic in origin. Thyroid transcription factor–1 (TTF–1) was positive in more than 80% of primary pulmonary adenocarcinomas and in none from the sites other than the thyroid. Mucinous bronchioalveolar carcinomas are usually negative. Immunocytochemistry with a panel of cytokeratins (CK) 7 and 20, along with TTF–1, is recommended for identification of the origin of adenocarcinoma in pulmonary cytology.

Objective: The aim of the study was to assess the value of TTF–1 reactivity in adenocarcinomas determined by immunocytochemistry in different pulmonary cytologic specimens.

Methods and Results: Cytologic specimens of 83 patients with adenocarcinomas were analyzed. Immunocytochemistry was performed with a panel of antibodies: TTF–1, CK7, CK20 in all cases and CK5/6 if necessary. The study included 17 different bronchoscopic samples (aspirates, brushes, transbronchial FNA), 14 transthoracic FNA, 27 pleural effusions and 25 FNA of peripheral lymph nodes. TTF–1 was positive in 26/83 (31.3%) and negative in 47/83 (68.7%) samples. All TTF–1 positive adenocarcinomas were also CK7 positive, thus being conclusive of pulmonary origin. In TTF–1 negative group, pulmonary origin was
proven in 10/57 (17.5%) adenocarcinomas, whereas 18/57 (31.6%) adenocarcinomas were metastatic; in 29/57 (50.9%) adenocarcinomas other diagnostic procedures failed to prove their origin. CK20 positivity with CK7 negativity was conclusive of metastatic gastrointestinal adenocarcinoma.

Discussion: Numerous reports support TTF–1 expression in adenocarcinoma as being highly specific for pulmonary origin, if thyroid is excluded. We were able to identify 36/83 (43.4%) adenocarcinomas as pulmonary adenocarcinomas. Among them, only 31.3% were TTF–1 positive. In our study, about 60% of adenocarcinomas with uncertain origin were in the groups of pleural effusions and lymph nodes. In these groups, cytologic diagnosis of adenocarcinoma often provided evidence of the carcinoma expansion, aggressive behavior and poor differentiation, and served as a guideline for patient management. In the studies of mixed pulmonary adenocarcinomas, TTF–1 expression was lower in poorly differentiated segments as well as in the areas with bronchioloalveolar pattern. One explanation for the high percentage of TTF–1 negative adenocarcinomas in our material is morphological selection of adenocarcinomas of presumably non–pulmonary origin before immunocytochemistry.

Conclusion: TTF–1 in a panel with cytokeratins is specific for differentiation of the origin of adenocarcinomas. TTF–1 negative finding in adenocarcinomas does not exclude pulmonary origin, but only points to other diagnostic procedures for definitive diagnosis.

Key words: thyroid transcription factor–1 (TTF–1), pulmonary adenocarcinoma

SUMMARY

CYTOMORPHOLOGY OF ACUTE MIXED LEUKEMIA

M. SUČIĆ, D. BATINIĆ, R. ZADRO1, S. MRSIĆ1 and B. LABAR2

Division of Cytology, University Department of Pathology and Cytology, 1Divisions of Immunology and Hematology and Molecular Hematology, Institute of Clinical Laboratory Diagnosis and 2Division of Hematology, University Department of Medicine, Zagreb University Hospital Center, Zagreb, Croatia

Biphenotypic acute leukemias (AL) with blasts expressing both myeloid and lymphoid antigens are grouped with undifferentiated AL and bilineal AL in the group of AL of ambiguous lineage. Not all AL with myeloid and lymphoid antigens (ALMy+Ly) are true biphenotypic AL. According to EGIL scoring system, true biphenotypic ALMy+Ly are those with a sum of antigens 2 or more points for both myeloid and lymphoid lineage or for B and T lineage.

The aim of this study was to compare cytomorphology and immunophenotype of AL to better understand the relation of certain AL morphology, immunophenotype, cytogenetics and molecular biology of biphenotypic AL.

Patients and Methods: The study included a group of 169 AL patients treated from 1985 till 1991, and a group of 102 AL patients treated from 1993 till 1996 at Zagreb University Hospital Center. Bone marrow and peripheral blood of the two groups of AL patients were analyzed according to Pappenheim (May–Grunwald–Giemsa), cytochemical and alkaline phosphatase–anti–alkaline phosphatase (APAAP) immunocytochemical staining. Flow cytometry immunophenotyping of bone marrow was also done in both patient groups.

Results and Discussion: In the group of 169 adult AL patients, 116 were cytomorphologically classified as acute myeloblastic leukemias (AML), 35 as acute lymphoblastic leukemias (ALL) and 18 as acute undifferentiated leukemias (ANLM). In 6 (3.4%) of 169 AL patients, blasts expressed both myeloid and lymphoid antigens. In the group of 102 AL patients there
were 19 (18.6%) ALMy+Ly. In 64 patients cytomorphologically classified into AML subgroup out of 102 AL patients, there were 15 (14.7%/102; 23.4%/64) AML with lymphoid antigens (AMLLy+). In 35 patients cytomorphologically diagnosed as ALL and 3 as ANLM out of 102 AL, there were 4 (3.9%/102; 10.5%/38) ALL with myeloid antigens (ALLMy+). The incidence of mixed AL in 102 AL was more consistent with other studies, pointing to the necessity of myeloperoxidase (MPO), CD7 and TdT determination as part of standard immunophenotyping for better recognition of mixed AL.

Conclusion: In both groups of 169 and 102 AL patients, the majority of AL cases were cytomorphologically classified as AML. In the group of 169 patients there were 5 AML Ly+ and in the group of 102 patients there were 15 AML Ly+. In one ANLM,My+ out of 169 AL and also one ANLM,My+ out of 102 AL, blasts were cytomorphologically undifferentiated; in 3 ALLMy+ of 102 AL blasts expressed lymphoid morphology. According to EGIL scoring system, among 15 AMLLy+ of 102 AL there were 4 true biphenotypic AL My+Ly (1 M1, 2 M3, 1 M4), and in 4 ALMy+Ly with undifferentiated and lymphoid morphology there were 2 true biphenotypic AL (1 L2; 1 ANLM). In 3 ALLB+T out of 35 ALL, one was interlineal biphenotypic AL. These observations are consistent with other studies and WHO determinations indicating that the majority of true biphenotypic leukemias are associated with immature monoblastic or myeloid cytomorphology or with lymphoid or undifferentiated characteristics, but may also express any AML cytomorphology type. Thus, there is no direct correlation of leukemic cell cytomorphology and biphenotypic AL immunophenotype.

Key words: mixed acute leukemia, AL cytomorphology; AL immunophenotype

SUMMARY
BIPHENOTYPIC AND BILINEAL ACUTE LEUKEMIAS
D. BATIŅIĆ, K. DUBRAVČIĆ, LJ. RAJIĆ1, M. MIKULIĆ2 and B. LABAR2
Division of Immunology & Referral Immunodiagnostics Center of the Croatian Ministry of Health and Welfare, Clinical Institute of Laboratory Diagnosis; 1Division of Hematooncology, University Department of Pediatrics, 2Division of Hematology, University Department of Medicine, Zagreb University Hospital Center, Zagreb, Croatia

Human acute leukemias (AL) are classified as myeloid or lymphoid according to cytomorphology and the expression of leukocyte differentiation antigens/CD–markers. However, in the minority of cases leukemic cells express markers of more than one lineage, which has led to the introduction of a new subgroup of acute leukemias termed mixed or biphenotypic acute leukemias (BAL). In an effort to distinguish between BAL and those AL with aberrant expression of markers of other lineage, the European Group for the Immunological Characterization of Acute Leukemias (EGIL) has proposed a scoring system in which CD–markers are assigned a score of 0.5, 1.0 or 2.0, depending on the specificity of a particular antigen for myeloid, B– and/or T–lymphoid lineage, respectively. The new WHO classification of hematologic tumors has adopted the EGIL criteria for BAL and introduced a new group of AL termed ‘AL of ambiguous lineage’. In addition to BAL in which a single cell population expresses both myeloid and lymphoid differentiation markers, this new group of leukemias also comprises cases that present with two separate blast populations (acute bilineal leukemia, aBLL). In general, BAL accounts for less than 5% of all AL cases, whereas aBLL is a rare disease constituting 1%–2% of AL cases that contains B— or T–lymphoid along with myeloid blasts. Chromosome abnormalities are frequent in both entities with a relatively high incidence of Philadelphia chromosome and rearrangements involving 11q23,
especially in cases with B– and myeloid involvement. Other biological features include CD34 expression and multi–drug resistance P–glycoprotein overexpression. The prognosis of BAL and aBLL is unfavorable, with poor prognostic factors being age, high WBC and the presence of Philadelphia chromosome. Unfortunately, optimal therapy is not known, although regimens designed for acute lymphoblastic leukemia may result in a better response rate. Collaborative studies are needed for better understanding of the biology of these entities and establishment of standard therapeutic protocols.

Key words: biphenotypic acute leukemia, immunophenotype, classification, diagnosis

SUMMARY
NEEDLE ASPIRATION CYTOLOGY OF THE BREAST: CURRENT PERSPECTIVE ON THE ROLE IN DIAGNOSIS AND MANAGEMENT
G. KOCJAN
Department of Cellular Pathology, London University College, London, UK
The aim of this review is to highlight the continuing role of fine needle aspiration cytology (FNAC) in the diagnosis of breast lesions, against a background of its diminishing use in some centres, particularly those involved in breast screening, because of its controversial inadequate rate and suboptimal accuracy. This review explores the current practice and confirms the continuing role of FNAC in the diagnosis and management of breast lesions. The three main areas where FNAC still plays a major role are the following: (a) diagnosis of benign disease in symptomatic palpable lumps as part of triple assessment; (b) staging of breast carcinoma, in particular preoperative axillary lymph node FNAC and intraoperative sentinel node imprints; and (c) diagnosis of metastatic disease at distant sites following treatment for carcinoma. Excision biopsy of the lesion to establish whether it is benign or malignant is not an acceptable mode of diagnosis any more. When triple assessment is concordant, final treatment may be ensued without open biopsy. Triple assessment is a cost effective, easy to perform and time saving approach, however, it can only be used at those institutions where excellent imaging facilities as well as services of a cytopathologist are available. The majority of European countries use similar reporting system for breast FNAC (C1–C5), in keeping with European guidelines for quality assurance in breast cancer screening and diagnosis. A clear reporting system ensures that an unequivocal cytological diagnosis of malignancy is reliable, and in cases where mammography/ultrasonography and clinical examination are in agreement with FNAC, frozen section examination is unnecessary. Suggested thresholds for cytology performance (where therapy is partially based on FNAC) according to the UK NHSBSP are the following: absolute sensitivity (C5 only) >70%, complete sensitivity (C3, C4, C5) >90%, specificity >65%, positive predictive value >99%, false negative <4%, false positive <0.5%, inadequate rate <15%, inadequate rate from cancers <5% and suspicious rate <15%. The issue of optimal sampling to obtain adequate cell material in sufficient quantity is of paramount importance when assessing the accuracy of FNAC. The inadequate rates in FNAC from different sources are lowest when FNAC is performed by a cytopathologist and highest when done by a non–cytopathologist. The multidisciplinary approach is necessary to amplify FNAC quality and to reduce its diagnostic limits. Only when this model of activity is not available, the role of FNAC is less effective and the addition of core biopsy (CB) to FNAC should be considered. CB as an alternative diagnostic modality should be used advisedly, in situations where it is more likely to yield diagnostic information, e.g., in the diagnosis of impalpable masses, microcalcifications or a clinically apparent malignancy where preoperative chemotherapy is planned. CB should not be used as a substitute for poor performance at FNAC. The methods are not mutually
exclusive. Where there is access to skilled cytopathologists, FNAC and CB can complement each other and provide a highly accurate, rapid and cost-effective means of patient triage. FNAC has an advantage of being an immediate and excellent method for on-site examination and one-stop diagnosis at breast outpatient clinics. Since the majority of patients attending a breast clinic have benign disease, they benefit from rapid diagnosis and discharge from the clinic. Sentinel node biopsy, now used routinely during the operation for breast carcinoma with the aim of achieving «one-step» surgery can be reduced by one third of patients who ultimately require axillary node dissection if preoperative image guided FNAC of the axilla is used. Positive intraoperative imprint cytology is a reliable tool for proceeding to axillary node dissection, the method having a very high specificity in all published series. FNAC remains the method of choice of diagnosing metastatic disease at extramammary sites. Hormone receptor status, but not HER 2, can be reliably assessed from cytological material. Cells carry a promise of molecular diagnosis and targeted treatment in the future. The future of breast FNAC is bright.

Key words: breast, aspiration cytology, breast carcinoma

SUMMARY

CURRENT APPROACH TO DIAGNOSIS AND TREATMENT OF ACUTE LEUKEMIA IN ADULTS

B. LABAR, D. NEMET, M. SUČIĆ1, D. BATINIĆ2, R. ZADRO2, S. MRSIĆ2, R. SERVENTI–SEIWERTH, D. SERTIĆ, M. MIKULIĆ and N. DURAKOVIĆ

Department of Hematology, University Department of Medicine, 1Department of Cytology, University Department of Pathology and 2University Department of Laboratory Diagnosis, Zagreb University Hospital Center, Zagreb, Croatia

Current classification of acute leukemia is based on morphology, immunophenotyping, cytogenetic and molecular abnormalities of leukemic cells. All these techniques have a diagnostic and prognostic value. Molecular abnormalities in many cases suggest the pathogenesis of acute leukemia, but also point to the key site of genetic abnormalities that may be targeted with the therapy. Treatment approach in acute leukemia is still chemotherapy. The probability of long-term disease-free survival after intensive chemotherapy for younger patients with acute lymphoblastic leukemia and acute myeloid leukemia is 30%–40% and 40%–50%, respectively. Allogeneic stem cell transplantation is associated with better disease-free survival compared to other cytotoxic regimens. In recent years, targeted therapy seems to improve the chemotherapy outcome. This therapy targets only leukemic cells while sparing normal cells. Immunotherapy, differential agents and especially drugs acting on the key molecular abnormalities are currently being used together with chemotherapy as a treatment approach for acute leukemia. It is expected that techniques such as gene expression profiling will identify genetic abnormalities and their proteins as a targeted site for new drugs. This might increase the efficacy of leukemia treatment and control.

Key words: acute leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, diagnosis, treatment
THE STORY ABOUT HODGKIN’S LYMPHOMA
S. OSTOJIĆ KOLONIĆ
Clinical Hematology, Department of Medicine, Merkur University Hospital, Zagreb, Croatia
The exciting story about Hodgkin’s lymphoma is 170 years old. Today, we know a lot about biology of this B cell neoplasma (derived from the germinative center), and the diagnostic standard criteria are clearly defined and accepted. Although the definition of prognostic factors for early disease varies between different study groups as well as the definition of advanced disease therapeutic aim is same for all clinicians: preserving the high cure rates while reducing the acute and long–term toxicities. Today, with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy followed by radiotherapy in some patients’ group, more than 85% patients can be cured. Maybe, the recently published results of the latest researches in Hodgkin’s lymphoma (evidence for the cancer stem cell; the role of T cells in tumour microenvironment in survival of lymphomas cells; the role of galectin–1 in tumor escape in Hodgkin’s lymphoma) will help us to reach our therapeutic goal: cure for all patients with Hodgkin’s lymphoma!

Key word: Hodgkin’s lymphoma

SUMMARY
DIFFUSE LUNG DISEASE — ADVANCES IN PATIENT MANAGEMENT
T. PEROŠ–GOLUBIČIĆ
Jordanovac University Hospital for Lung Diseases, Zagreb, Croatia
Diffuse lung diseases (DLD), known as interstitial lung diseases or diffuse parenchymal lung diseases, are a large group of disorders of diverse etiology and causes, however, sharing similar clinical, radiological and pathophysiological characteristics. In the last fifteen years, DLD have attracted considerable interest of medical society. During that period, a consensus of the British Thoracic Society on the Diffuse Parenchymal Lung Disease and Statement of the American Thoracic Society (ATS) and European Respiratory Society (ERS) on idiopathic pulmonary fibrosis, idiopathic interstitial pneumonias and sarcoidosis have helped precisely define certain phenotypes. The newly developed technique of high resolution computed tomography, which can show finest details of lung parenchyma, has also helped precisely define diverse entities, which have aroused interest among molecular biologists and genetic researchers with a goal to define the etiology, pathogenesis and progression of these diseases. The renaissance of interest in this scientific field has also stimulated pharmaceutical industry to enhance its activity, which has resulted in intensified research of potentially new drugs, especially for fibrotic lung processes such as idiopathic pulmonary fibrosis. The disease outcome is very difficult to estimate in these, most often chronic diseases; however, it is very important to achieve the best possible if not the same quality of life as before the disease onset. Different questionnaires have been used and the results were not always as expected; for instance, worsened lung function tests were not most important in defining the quality of life. These vivacious activities have stimulated us to present to the patient and diligent reader recent advances in the management of DLD patient; the article is mostly dedicated to recent advances made in diagnostic procedures, hoping for a comparable success to be achieved in therapeutic approach.

Key words: diffuse lung disease, interstitial lung disease
SUMMARY
HISTOPATHOLOGIC DIAGNOSIS OF LUMINAL AND BASAL TYPE BREAST CANCER
B. ŠARČEVIĆ
Department of Pathology, University Hospital for Tumors, Zagreb, Croatia
Despite tremendous advances in breast cancer characterization and therapy over the last 20 years, clinicians still have difficulty to accurately predict the prognosis in individual breast cancer patients. Patients with identical histologic tumor characteristics can have markedly different outcome in terms of distant metastasis–free and overall survival. The most common breast cancer is invasive ductal carcinoma, which is heterogeneous and according to immunohistochemical markers is divided in the luminal and basal type, as also identified by the recent expression profiling method. Microarray expression profiling is a novel method to further characterize breast cancer tumors at the gene expression level. Breast cancer subtypes have been described which display different biological behaviors. In addition, groups of genes known as gene–signatures have been identified, which provide more accurate prognostic factors than current clinical and histologic features. Future clinical decisions may rely on expression profiling of breast tumors.

Key words: breast cancer, molecular profiling, tissue microarray

SUMMARY
THE VALUE OF TRANSBRONCHIAL NEEDLE ASPIRATION COMBINED WITH RAPID ON–SITE EVALUATION
N. CHALFE1 and S. SMOJVER–JEŽEK2
Departments of 1Bronchoscopy and 2Cytology, Jordanovac University Hospital for Lung Diseases, Zagreb, Croatia
The samples obtained by transbronchial needle aspiration (TBNA) during fiberoptic bronchoscopy (FOB) are suitable for rapid on–site evaluation (ROSE). Availability of on–site results may increase the effectiveness of FOB. This study prospectively investigated the diagnostic range, yield and practical value of this technique.

Methods and Results: Consecutive patients with radiologically suitable mediastinal mass lesions or lymph nodes on conventional chest x–rays and lung CT scans were investigated with FOB. TBNA–ROSE was performed during FOB. A cytopathologist prepared unstained slides, stained them and evaluated the aspirates on–site and notified the bronchoscopist about the necessity of further sampling. If adequate diagnostic material was collected with TBNA, the provisional diagnosis was noted and the procedure ended. Fifty patients with mediastinal masses or lymph nodes were included. In 37 (74%) patients, the diagnosis was made on–site: non small cell lung cancer in 16, small cell lung cancer in 4, metastatic cancer in 6, granulomatous disease in 9 and lymphoma in 2 patients. TBNA was not diagnostic in 9 (18%) patients with reactive lymphoid hyperplasia that required additional studies. Overall, ROSE shortened bronchoscopic sampling in 74% of patients. The mean intervention time was 25 minutes. No side effects of TBNA were observed.
Conclusion: TBNA combined with ROSE is safe and highly effective. ROSE increased the sensitivity of TBNA.
Key words: fiberoptic bronchoscopy, transbronchial needle aspiration, rapid on–site evaluation