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# A review of the 5th World Congress on Lung Cancer held by the International Association for the Study of Lung Cancer.

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The fifth World Congress of the International Association for the Study of Lung Cancer (IASCLC) took place in Interlaken, Switzerland in August 1988. As at the earlier congresses a comprehensive view of the current status of lung cancer in epidemiological, biological, and clinical research terms was presented. The present review will briefly identify current and future trends in the study of lung cancer, extracted from more than 750 presented papers [1].

## Epidemiology, Etiology, and Prevention

The relation between tobacco smoking and lung cancer is firmly established, with changes in incidence pattern paralleling alterations in smoking habits 15–20 years ago. Other carcinogenic exposures during work or at home, such as alpha particle emitting radon daughters, can increase the risk several-fold, probably acting synergistically with cigarette smoke, as was earlier demonstrated with asbestos. By employing modern epidemiologic calculations to changes in current incidence rates, equalization between sexes in the incidence of lung cancer is predicted early in the 21st century. In the industrialised world there is a marked increase in women and a slight decrease in men. In most developing countries the uncontrolled expansion of tobacco use is setting the stage for a future epidemic of smoking-related diseases. A dramatic increase in lung cancer incidence in developing countries is already present.

The interesting observation that the majority of smokers do not develop lung cancer might be explained by a complex series of pathogenetic events, including, in addition to carcinogenic exposures, specific chromosomal and DNA changes, oncogene activation, autocrine growth factor stimulation, and apparently also inherited genetic changes. The latter are circumstantially evidenced by mendelian pedigree analysis and the observation of a strong correlation between certain metabolic phenotypes and the development of lung cancer.

A protective effect of carotenoids, by their ability to inactivate radicals and to inhibit proliferation, has been noticed for several years. Other dietary factors are considered possible risk factors but are only at an early stage of investigation. Large scale trials on chemoprevention by oral beta-carotene and vitamin E *versus* placebo are ongoing, and by the early 1990's some conclusions should be available. It is agreed that at least 80% of all lung cancers are caused by tobacco and thus preventable by smoking abstinence. Physicians are urged to take an active role in programs directed against the use of tobacco at national and individual level.

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## Histopathological classification

The current international classification is still based on light microscopic criteria published in the latest revision of the World Health Organizaiton (WHO) classification of 1981. From a clinical point of view the most important issue is still to separate small cell carcinomas from non-small cell carcinomas. Recent findings in pathology and biology have demonstrated that morphologic transitions from one type to another take place, making histopathological typing and subtyping difficult.

### *a. Small cell carcinoma (SCLC)*

According to the WHO classification SCLC is morphologically subclassified into three subtypes: "Oat-cell" type, "Intermediate" type (including also mixed small cell/large cell morphology), and "Combined" type, which includes SCLC in combination with squamous cell and/or adenocarcinomas. Patients with tumours of SCLC/large cell morphology have earlier been found to have a poorer prognosis compared to pure SCLC, but nevertheless better than NSCLC. The SCLC classification was recently modified by the IASCL (Hirsch *et al.*, CANCER 62: 973–977, 1988) to compose three more easily defined groups: a) pure SCLC, b) mixed SCLC-large cell, and c) combined subtype, same as before. This recommendation, being simpler, should facilitate uniformity in diagnosis and reporting of SCLC.

A study by Aisner *et al.* (Baltimore, USA) was presented, in which the prognostic implication of SCLC/large cell morphology was evaluated in patients with extensive disease. In 10 patients (2%) with tumours of this specific morphological variant no difference was observed in response or survival when compared to patients with pure SCLC. The lack of agreement

earlier findings might reflect some important interobserver problems in the interpretation of large cell components, which need to be solved in future prospective studies.

*b. Non small cell carcinomas (NSCLC)*

The reliability of multi-institutional biopsy diagnosis and the interobserver problem in NSCLC protocols was presented by Yesner *et al.* (New Haven, USA), based on 584 biopsies. The study demonstrated clearly the need for a central histopathological review, especially for poorly differentiated tumours and large cell carcinomas.

During the last decade great developments have occurred in the field of immunocytochemistry using polyclonal and monoclonal antibodies. Severeral studies on immunocytochemical markers for histopathological diagnosis were presented. When applying neuroendocrine markers (*i.e.* neuron-specific enolase, chromogranin, synaptophysin, etc.) overlap was noted between SCLC and NSCLC tumours. The clinical impact of the neuroendocrine (NE) differentiation in NSCLC is not clear: Berendsen *et al.* (Groningen, NL) found no prognostic influence in 141 prospectively analysed NSCLC patients, but the presence of NE markers in a small series of NSCLC seem to be associated with higher response rates than the approximately 20% for all other NSCLC patients.

The clinical implication of histological subtyping of adenocarcinoma according to the WHO criteria was analyzed by Sorensen *et al.* (Copenhagen DK) in 259 consecutive patients. The smallest subgroup, the bronchioloalveolar carcinoma, constituted only 7% but with a prognosis more favourable than for the other subtypes *i.e.* acinar adenocarcinoma (50%), papillary adenocarcinoma (9%), and solid carcinoma with mucus formation (12%).

The relevance of this sub-category is still a subject for debate, (Kimula *et al.*, Kanegawa, Japan), but as the histological criteria define a group with a particular prognosis, the subtyping seems appropriate.

Recent studies have looked at the role of DNA ploidy, demonstrated by DNA flow cytometry, in the prognostication of malignant lung tumours. The ploidy of 87 resected lung tumours was presented by Hawson *et al.* (Brisbane, Australia) and correlated with the degree of histological differentiation. It was concluded that ploidy is not a means of quantitation of the degree of histological differentiation, but it provided additional prognostic information. In 1987, aneuploidy was suggested by the same investigators (Lancet 1987 (ii): 530–533) to be an independent negative prognostic factor in NSCLC patients. This finding is now corroborated by other studies. Relapse after surgery was shown to be strongly correlated with the degree of aneuploidy in the surgical material by several investigators.

Morphologically bronchial carcinoids cover a wide range from benign to malignant tumours, the latter very close to small cell carcinomas. The role of DNA ploidy in this tumour was correlated to survival by Hasleton *et al.* (Manchester, UK) in 43 patients. The five year survival was 84% for patients with diploid tumours and only 58% in the aneuploid cases (p=0.052). In a Cox multivariate regression analysis including other histological variables, the DNA ploidy, did not provide any independent prognostic information.

## Biology of malignant lung tumours.

In recent years an increasing number of biological studies have been performed on surgical material as well as cell lines and heterotransplants. Focus has been laid on the interrelationship between the major histological types.

*a. Oncogenes*

Oncogenes have been shown to undergo genetic changes in lung cancer cells, including point mutations in the *ras* family and often a considerable amplification of the *myc* family of cellular proto-oncogenes (including *c-myc*, N-*myc*, and L-*myc*). *In vitro* studies on SCLC lines demonstrate that high level expression of *c-myc* gene is associated with faster growth and higher cloning efficiency and a change in morphology to a large cell/SCLC appearance. The L-*myc* was initially discovered in SCLC, but later also found expressed in NSCLC. The role of oncogenes in the pathogenesis of malignant lung disease and their clinical value is still unclear.

*b. Chromosomal abnormalities*

Several cytogenetic studies have found various chromosomal changes in lung cancer. By the development of restriction fragment length polymorphism (RFLP) technology, true loss of DNA from the tumour cells has been demonstrated. The most prominent abnormality is deletion of the short arm of chromosome 3. This deletion is found in all cell types of lung cancer, suggesting that the abnormality is a common requisite for the development of lung cancer or is perhaps an early step in pathogenesis. The findings of 3 p-deletions in all types of lung cancer agrees with the concept that the different histological types of lung cancer originate from one common malignantly transformed stem cell population in which different histological characteristics reflect preferentially expressed differentiation pathways.

*c. Growth factors*

From *in vitro* studies several substances have been identified as autocrine growth factors in SCLC. Much interest is directed at the hormone gastrin releasing peptide (GRP, mammalian bombesin). High levels of bombesin-like immunoreactivity have been demonstrated

in bronchial lavage fluids of smokers, suggesting a possible role in the pathogenesis of lung cancer.

Another autocrine growth factor in SCLC is insulin-like growth factor I (IGF I, somatomedin). *In vitro* studies were presented in which the stimulatory effect was inhibited by anti-IGF I.

Epidermoid growth factor (EGF) stimulates proliferation of NSCLC cell probably *via* EGF-receptors. Studies by Rotsch *et al.* (Marburg, FRG) suggest that EGF-receptors play a role in tumour growth control by an autocrine mechanism.

*d. Monoclonal antibodies*

The field of monoclonal antibodies (Moab) has developed almost exponentially including Moab's with more or less specificity against malignant lung tumours, especially SCLC. Antibodies have been raised against intracellular antigens (intermediate filaments and enzymes) and to antigens associated with the cell membrane of the lung tumour cells. Most of the known Moab's identify antigens present on a wide range of epithelial tumours and normal epithelial cells. SCLC antibodies indentify epithelial antigens and antigens related to neuroendocrine differentiation. The latter are also expressed in normal and malignant neuroendocrine tissues and seem useful mainly in distinguishing SCLC from NSCLC. This area however has been rather confusing since quite often the antibodies are not very well characterized and the definition of the epitopes which they recognize is also poor.

In order to make a uniform characterization of the antibodies developed in several different laboratories an IASLC workshop on SCLC antigens was held in London in 1987, and the consensus was presented in Interlaken [2]. It succeeded to cluster the antibodies according to their characterization and specificity, and follow up studies including clinical trials are ongoing.

Moab's against antigens with different expression in tumour cells and haemopoietic tissues have been used in SCLC to detect bone marrow metastases not detectable by conventional histology. Whether such findings mean the same as metastases demonstrated by light microscopy, and with the same prognostic implications for the patients, is uncertain.

## Prognostic factors and clinical assessemnt

*a. SCLC*

The role of NSE (neuron specific enolase) serum concentration as a prognostic determinant was evaluated in several papers, all suggesting a considerable value of this biochemical marker. The prognostic influence of elevated lactate dehydrogenase (LDH) and of NSE in serum was strongly correlated in a Cox multivariate analysis of 86 patients (Osterlind *et al.*, Copenhagen, DK). NSE forced LDH out of the prognostic model, being the most sensitive prognostic determinant in SCLC at present.

While gastrin releasing peptide (GRP), which is frequently present in SCLC tissue, is rarely elevated in serum, the precursor, pro-GRP, is significantly elevated in blood samples from patients with SCLC when compared with NSCLC, chronic lung diseases, and normals. The prognostic influence of this potential marker molecule has yet to be evaluated.

Several other peptides are proposed as possible diagnostic and prognostic markers for SCLC, but await further evaluation.

A tendency towards non-invasiveness in staging has questioned the role of bone narrow examination (BME). Several studies suggest BME should be omitted, arguing: a) The bone marrow as the sole metastatic disease site is demonstrated in very few patients, and b) imaging procedures today are more sensitive and have less morbidity.

A very sensitive detection of bone marrow metastases with magnetic resonance imaging (MRI) was presented by Carney *et al.* (Dublin, Ireland). The positive findings were not histologically verified. In the detection of intra-abdominal metastases from SCLC the CT-scan was found to be superior to ultrasound (US). It was emphasized that positive findings, still need histological confirmation, ideally obtained by ultra sound guided biopsy.

*b. Non-SCLC*

A prognostic evaluation of clinical parameters in adenocarcinoma was presented. In a multivariate analysis for poor performance status (PS), no surgical resection, leukocytosis, high LDH and liver metastases predicted a poor prognosis. Response to chemotherapy, on the other hand, did not predict a particularly good prognosis. This study provides a clinically useful stratification model based on easily available data.

The prognostic implications of DNA flow cytometric analysis of resected NSCLC tissue was mentioned earlier.

## Surgery

The application of surgery in several $T_3$ and even $T_4$ tumours now seems feasible due to refined methods and new techniques including lasers. The relative impact of these improvements remains small but crucial for a large number of patients with localised NSCLC at the edge of resectability as the prospect is potential cure by surgery *versus* transient palliation at the cost of considerable toxicity.

Adjuvant and neoadjuvant chemotherapy in NSCLC was the subject of several investigations. The aim of neoadjuvant therapy is to reduce an initially unresectable local tumour to a lower T category. Data from prospective evaluations of randomised patients are not yet available, and only feasibility studies with selected patients were presented.

No new data was presented on the role of surgery in the management of SCLC.

## Chemotherapy.

*a) Choice of drugs in SCLC - Any standard chemotherapy?*

More than 6000 patients were included in the vast number of papers on chemotherapy for SCLC. The new platinum compound carboplatin (JM-8) has high activity according to an increasing number of published regimens. The most frequently applied cytostatic agent was etoposide (VP-16) in various combinations. There were no further data to identify the specific combination to be considered as standard.

The rather old cytostatic agents teniposide and ifosfamide have regained much interest and are currently under evaluation in different combinations. No new agent of high activity was presented. The orally administered nitrousurea derivative tauromustine (TCNU) yielded response in 3 of 15 evaluable, previously untreated patients (Bowman *et al.*, Edingburgh, UK), while lonidamide (a new cytotoxic agent without haematological toxicity) appeared not to improve survival and response rates in combination with VP-16 and cisplatin (Evans *et al.*, Toronto, Canada).

The phase II trials presented, did not include previously treated patients, whereas in the previous world congress in Toronto, 1985, virtually all did.

*b) Scheduling and duration*

Only a single trial contributed to the evaluation of alternating *versus* continuous chemotherapy (Fukuoka *et al.*, Tokyo, Japan). Cyclophosphamide, doxorubicine, and vincristine (CAV) alternating with cisplatin and VP-16 (PE) produced a higher overall response rate than CAV alone, while PE and CAV-PE did not differ significantly. The clarification of whether the improved results are related to alternation or to the introduction of more active drugs (PE) awaits further analysis.

Treatment duration or the number of cycles required to produce optimal results is uncertain. There is an obvious trend towards a shortening of the therapy but some limitations are now recognised. A large randomised comparison by Harper *et al.* (London, UK) of long *versus* short induction, with or without further therapy on relapse, found a significantly worse survival with the shortest strategy of 4 courses and no eventual chemotherapy.

A new approach, an "as required" strategy, was preliminarily reported in comparison with planned chemotherapy (Spiro *et al.*, London, UK). The patients were randomized to receive chemotherapy only when progressing and for symptom control, or planned chemotherapy in 8 courses. The "as required" patients received fewer cycles of chemotherapy than the controls, and scored less favourably than the patients in the regular treatment arm in a quality of life (QL) assessment. This difference was to be anticipated, as in the study arm chemotherapy was given only at the appearance of symptoms and/or disease progression, while these incidents were temporarily avoided in at least some of the patients in the control arm.

Disease progression as well as toxicity is related to a reduced "quality of life" score. In a prospective quality of life analysis during chemotherapy, including a comprehensive somatic, social and psychological assessment of 98 SCLC patients, improvement in quality of life was demonstrated in responders and in patients who survived more than 6 months. These studies document that until relapse, the quality of life of patients with SCLC improves during intensive chemotherapy when response is achieved.

The important implication of these observations is that QL assessment is now both reproducible and sensitive so that investigational and clinical use may be warranted. As pointed out by several authors, scales measuring QL assess different aspects but they are more or less correlated with each other. There is a need for standards in the assessment and reporting of quality of life in trial patients.

*c) Central nervous system*

Complete responses on CT scans of the brain and subsequent neurological alleviation after induction chemotherapy were reported by several investigators suggesting that initial brain metastases respond to chemotherapy as frequently as do metastatic SCLC in other sites. The studies were all rather small and the intensity as well as the length of follow up varied. Glucocorticoid therapy has been suspected of obscuring radiological evaluation of brain tumours and also to reduce their uptake of chemotherapeutic substances. The impact of this adversity is questionable as 80–100% of patients with initial brain metastases and 30–40% with relapse brain metastases, have responded on systemic treatment alone, in spite of concurrent steroid therapy in most cases. Activity of high-dose etoposide against meningeal carcinomatosis in five of seven SCLC patients was also reported. The duration of CNS response after chemotherapy was, when reported, 4–5 months in median, which is in the same range as the results obtained with additional radiotherapy. The duration parameter is not generally reported as some studies added cranial irradiation after assessment of primary response to 3 or 4 cycles of chemotherapy.

*d) Biological response modifiers*

Interferons have been evaluated in several studies in recent years with no affirmative results for lung cancer. A single study of alpha-interferon *versus* combination chemotherapy *versus* no treatment as maintenance after response to combination CT in SCLC (Mattson *et al.*, Helsinki, SF) has not reached the conventional levels of of significance, so any suggestion of a role for interferon in maintenance therapy awaits further observation and accrual of patients in the study.

Colony stimulating factors (CSF's) stimulate the bone marrow and are thus considered as possible

adjuvants to myelosuppressive chemotherapy by reducing haematological toxicity and facilitating further intensification of dose. Bronchud *et al.* (UK) reported on 12 SCLC patients treated with continuous infusion of G-CSF during combination chemotherapy. An increase in neutrophil counts and no side effects were observed. Similar findings were reported by others. Further evaluation at the phase I and II level is needed.

*e) Non-SCLC*

The overall results in this group were dismal. Whether cytostatic treatment is superior to best supportive care in survival and quality of life was not convincingly clarified. A preliminary report on quality of life assessment of NSCLC patients in a randomized trail, was presented by Ahmedzai *et al.* (Leicester, UK). At three months patients treated only palliatively scored slightly worse than the patients in two treatment arms. No difference was seen at six months. A transient improvement of QL in spite of poor objective response seemed to occur in patients actively treated.

## Radiotherapy

No new trials on chemotherapy *versus* chemotherapy + radiotherapy in SCLC were presented. The matter was dealt with in reviews only. Prophylactic cranial irradiation (PCI) is widely applied but a more critical attitude towards its use seems to have developed in recent years. Single dose PCI, which has not been discussed before, was proposed by Stout *et al.* (Manchester, UK). In the combined modality approach (chemotherapy and radiotherapy), an alternating schedule seemed to produce the best results with acceptable toxicity.

In both SCLC and NSCLC altered fractionation schemes were presented. A controlled hypo-fractionation study of palliative thoracic radiotherapy (RT) given in two *versus* 6–10 fractions found comparable effect, toxicity and survival in the two groups (Bleehen *et al.*, Cambridge, UK). The two fraction course of 8.5 GY two times 1 week apart is recommended. It remains open how patients would have faired in a third arm with no RT.

A hyper-fractionation approach applying multiple daily fractions (MDF) has yet to demonstrate its advantages.

All aspects of this congress were very well organised. The small size as well as the beautiful location of Interlaken made the atmosphere of the event unique. Melbourne, Australia, will host the next (sixth) world congress, November 9–14, 1991.

## References

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2. Souhami RL, Beverly PCL, Bobrow L (eds.) – Proceedings of the first international workshop on SCLC antigens. *Lung Cancer*, 4, No 1–2, p.1–116, 1988.