



1st European Lung Cancer Conference

Report

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Introduction

The International Association for the Study of Lung Cancer (IASLC) and the European Society for Medical Oncology (ESMO) organized the 1st European Lung Cancer Conference, 23 – 26 April 2008 in Geneva, which was a great success with over 1300 participants from over 70 countries. More than 30 years after their foundation the two societies have joined forces to hold biennial meetings presenting the cutting edge of clinical and translational research in a multidisciplinary scientific event.



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This report will present first an overview of the conference educational program and will conclude with a brief summary of the scientific presentations.

Lung cancer: a man-made disease

During the conference opening ceremony Heine H. Hansen received the IASLC-ESMO Lifetime Achievement Award. Paul Bunn said that through work and research in the lung cancer field H. H. Hansen has achieved great national and international esteem. He has held significant posts as President and Executive Director of both ESMO and IASLC. Throughout his career he has had a strong influence on the medical oncology specialty as inspirator and catalyst. Speaking after receiving the award, H. H. Hansen said that the history of lung cancer is closely related to the tobacco plant, which is native only to the Americas. Estimates of its dates of cultivation in the Peruvian/Equadorian Andes range from 5,000 to 3,000 BC, from where its use spread northwards on the American continent and later to Europe.

Tobacco policy

D.W. Bettcher spoke about World Health Organization (WHO) efforts in collaboration with global partners to work with countries on the implementation of a package of six cost-effective policies that build on demand reduction measures: raising tobacco taxes and prices; enforcing bans on tobacco advertising, promotion and sponsorship; warning people about the dangers of tobacco; protecting people from tobacco smoke in public places and workplaces; offering help to people who want to stop using tobacco; and monitoring successes and challenges.

Thoracic neoplasms and biomarkers in body fluids

H. I. Pass said that inability, specifically in lung cancer, to obtain tissue easily leads investigators to explore the use of serum, plasma, pleural effusion, sputum, and occasionally urine for biomarker discovery. Novel lung cancer markers include methylation profiles in the serum and the sputum, and the annexins. Innovative platforms which are now beginning to extend to fluids includes the profiling of glycosylated moieties, circulating RNA expression profiles, and microRNA profiles. Some of the novel markers including osteopontin may have both early detection and prognostication potential.

IASLC Lung Cancer Staging Project

Data on 100,869 patients with lung cancer, diagnosed between 1990 and 2000, were submitted to the IASLC database from 20 countries and 45 databases of different natures (registries, clinical trials, series, consortia). The recommendations of the T, N and M descriptors sub-committees have been submitted with the aim to propose changes in the seventh edition of the TNM classification for lung cancer (2009).

T stage

R. Rami-Porta reported that data for 18,198 of these patients fulfilled the inclusion criteria for the T component analysis. Recommended changes in the T classification are:

- to subclassify T1 into T1a and T1b
- to subclassify T2 into T2a and T2b
- to reclassify T2c as T3
- to reclassify additional nodule(s) in the same lobe as T3
- to reclassify nodule(s) in the ipsilateral non-primary lobe as T4 and
- to reclassify malignant pleural or pericardial effusion as M1.

M stage

P. E. Postmus reported that 5,592 selected T4M0 and M1 patients fulfilled the inclusion criteria for the analysis. Revisions should include grouping cases with malignant pleural effusions and cases with nodules in the contralateral lung in the M1a category, and cases with distant metastases should be designated M1b. In addition, cases with nodule(s) in the ipsilateral lung (non-primary lobe), currently staged M1, should be reclassified as T4M0.

Grouping

P. Goldstraw reported that several proposed stage groupings were created by combining adjacent groups. The proposed changes to the stage groupings are as follows:

- Incorporate proposed changes to T and M (affects T2, T3, T4 and M1 categories)
- Reclassify T2aN1 tumors (<=5 cm) as stage IIA (from IIB)
- Reclassify T2bN0 tumors (>5-7 cm) as stage IIA (from IB)
- Reclassify T4N0 and T4N1 tumors as stage IIIA (from IIIB).

Interventional endoscopy

M. Noppen provided an excellent overview of endoscopic procedures: development of new (e.g. electromagnetic navigation) and optimization of existing techniques (e.g. rapid on-site evaluation) increase the yield of diagnostic bronchoscopy; real-time endobronchial and esophageal ultrasound will change the staging algorithms.

Endoscopic management of carcinoma in situ

R. M. Huber reported that because pre-invasive or micro-invasive lesions are usually centrally located, surgery is a major procedure for these patients. There are existing data with photodynamic therapy (PDT), Nd-YAG laser therapy, electro-cauterization, cryotherapy and argon plasma coagulation.

Bronchoscopic treatment (BT) has a curative potential for patients with intra-luminal microinvasive radiographically occult lung cancer. Success rates with

BT have been in the 90–100% range, translating itself to local cure due to the reported follow-up time of >5 years. The best evidence exists for PDT with about 70% primary complete responses in larger series and in experienced centers 90% cancer-specific survival can be obtained.

Imaging for screening

R. J. van Klaveren provided a 10-step approach for routinely detected non-calcified pulmonary nodules (NCN) on a multi-detector computed tomography (CT; MDCT) in healthy persons. Recommendations are primarily based on individual cancer risk, the presence or absence of calcifications and nodule size.

- For nodules > 4-5 mm additional nodule characteristics should be taken into account.
- For nodules < 4 mm, a follow-up CT at 12 months is recommended in high-risk persons, whilst for low-risk persons no follow-up is needed. If no growth is observed at 12 months, no further follow-up is required.
- For solid, smooth or attached indeterminate NCN between 5-10 mm, an annual repeat scan is recommended, whilst for purely intra-parenchymal nodules a 3-month repeat scan should be made to assess growth.
- Growing lesions with a volume doubling time <400 days require further work-up and diagnosis, otherwise an annual repeat scan is recommended.

Staging the mediastinum

P. De Leyn said that in primary staging, mediastinoscopy remains the gold standard for the superior mediastinal lymph nodes (LN). Ultrasound-guided bronchoscopy with fine-needle aspiration (FNA) and endoscopic esophageal ultrasound-guided FNA are techniques that also provide cyto-histological diagnosis and are minimally invasive and complementary to mediastinoscopy.

In patients with potentially resectable N2 disease, mediastinoscopy has several advantages over endoscopic FNA. For restaging, invasive techniques provide cyto-histological information and are advisable despite the encouraging results with the use of re-positron emission tomography (PET)/CT imaging.

M. Krasnik reported that with the endobronchial ultrasound guided (EBUS) TB-FNA, it is possible to target lesions in the anterior mediastinum and the hilar regions not reachable with endoscopic ultrasound guided (EUS)-FNA, so theoretically the whole mediastinum can be examined.

Role of PET in staging and restaging

J. Vansteenkiste reported that loco-regional lymph node staging by fluoro-deoxyglucose (FDG)-PET is significantly superior to CT, with a negative predictive value equal or even superior to mediastinoscopy. FDG-PET also improves

extrathoracic staging. In truly integrated PET-CT, a combined scanner creates both datasets, subsequently merged to a single image. The most significant improvement by integrated PET-CT relates to the accuracy of T staging (more precise evaluation of chest wall and mediastinal infiltration or correct differentiation between tumor and peri-tumoral inflammation or atelectasis), rather than N-staging.

Adenocarcinoma sub-classification

W. Travis reported that searching for a clinically and biologically meaningful way to further characterize the mixed subtype adenocarcinomas needs to be based on careful attention to the histological criteria. Most articles focus mostly on bronchioloalveolar carcinoma (BAC), comparing this with all other adenocarcinomas. Several investigators showed a lack of association of epidermal growth factor receptor (EGFR) mutation with BAC subtype suggesting an association with invasive adenocarcinomas rather than BAC. One study found a dominant papillary subtype is a significant predictor of response to gefitinib. K-ras mutations are associated with mucinous BAC.

Early non-small cell lung cancer (NSCLC)

B. Passlick said that segmentectomies can be performed with equal results compared with those with lobectomy in lesions <1 cm. Only in the upper parts of the lung, should segmentectomies not be performed due to a higher local recurrence. In patients with early central lung tumors bronchoplastic procedures such as sleeve segmentectomies can be performed in order to preserve as much lung tissue as possible.

G. Scagliotti discussed the use of adjuvant chemotherapy in stage I NSCLC, advising that it should be restricted to clinical trials that evaluate the potential for refining and individualizing the treatment of early stage and improving the efficacy of cytotoxic chemotherapy.

D. H. Johnson reported that the application of pharmacogenomics has the potential to profoundly influence outcomes and improve overall survival in early lung cancers. In resected early stage NSCLC, patients with tumors overexpressing ERCC1 protein do not appear to benefit from platinum-based adjuvant chemotherapy. Preclinical studies and two recently completed clinical studies support the potential predictive value of ribonucleotide reductase M1 (RRM1) on gemcitabine efficacy. High levels of class III beta-tubulin are associated with taxane resistance. Thymidylate synthase (TS) mRNA levels and protein levels have been shown to be significantly higher in squamous cell carcinomas (SCC) of the lung compared with adenocarcinomas and influence the response to pemetrexed.

How to minimize the toxicity of radiotherapy

S. Senan discussed two approaches that can decrease toxicity of radiotherapy: the use of involved-field radiotherapy (IFRT)

as standard, and routine use of individualized radiotherapy planning using 4-dimensional CT (4-DCT) scans. The risk of radiation pneumonitis can be estimated using the V20, the percentage volume of normal lung minus the planning target volume which receives doses of 20 Gy or more. Measures to minimize the deleterious impact of high-grade esophagitis include referral to a dietician prior to commencing treatment, careful monitoring of body weight twice weekly, aggressive symptomatic treatment with analgesics, proton pump inhibitors, and early placement of feeding tubes in high-risk patients.

A promising approach is respiration-gated radiotherapy (RGRT), which permits a reduction in field sizes, as irradiation can be limited to phases in which the mobile target volume is in a predetermined position.

Stereotactic body radiation therapy for NSCLC patients

J. Belderbos informed the conference that stereotactic body radiation therapy (SBRT) is characterized by one or a few fractions with a high dose per fraction and a high geometrical accuracy. Factors influencing treatment outcome after SBRT are tumor volume (T1 vs. T2), the dose prescribed and tumor location. The SBRT is an effective treatment with high local tumor control rates >90% in patients with inoperable stage I NSCLC.

Radiofrequency

A. Gangi discussed recent reports on radio frequency (RF) ablation in the lung. Tumors had to be located more than 1 cm from the hilum, with no invasion of the soft tissues or mediastinum.

Malignancy has to be histologically proven for pulmonary nodules in patients with no history of cancer outside the lung. Targeted lung tumors in patients with a known distant history of cancer have to either be histologically proven or demonstrate a change in size of at least 25% in their largest diameter at CT at some time during the previous year of follow-up imaging.

Palliative RF ablation is performed in patients with painful chest wall lesions and in these cases the size could exceed four centimeters. The procedures are performed under CT scan guidance. Complete ablation is achieved in 80% of cases with tumors less than 4 cm. The best results are obtained with tumors less than 3 cm in diameter. The main adverse event is a pneumothorax which occurred in 50% of procedures, but a chest tube is required in only 5% of procedures.

Current therapy of stage IV NSCLC, moving towards personalized medicine

D. R. Gandara focused primarily on biomarkers relevant to platinum compounds and anti-microtubule agents and described the results of pilot studies and the first randomized prospective trials testing the concept, including limitations in the clinical setting.

Scientific Program Overview

Over 200 abstracts were presented during the conference containing much new scientific data. Some highlights are summarized below:

- S. Murray has generated a free-access online analytical database of somatic EGFR mutations in NSCLC. Updates and direct submissions to the online site (www.egfr-mutations.org) are encouraged, as are comments and suggestions.
- L. Crinò evaluated tumors from 130 surgical NSCLC patients for insulin-like growth factor receptor 1 (IGFR-1) and EGFR expression. IGFR-1 protein over-expression was detected by immunohistochemistry in 36% of patients and was associated with larger tumor size ($P=0.04$) but not with other clinical or biological characteristics. EGFR protein over-expression was observed in 55.2% of patients, more frequently in squamous cell carcinoma (SCC) than non-SCC (63.7% vs. 36.3%, $P=0.001$). IGFR-1 protein expression was associated with EGFR protein expression ($P=0.03$). At multivariate analysis, the co-expression of both IGFR-1 and EGFR emerged as an independent factor for shorter disease-free survival (DFS) ($P=0.01$).
- R. Rosell carried out a study in 93 patients with lung adenocarcinoma or large-cell carcinoma who were screened for EGFR D746-750 deletion and L858R mut and BRCA1 mRNA expression. 15 patients with EGFR mut received erlotinib; 78 without mut received chemotherapy according to BRCA1 levels (low: gemcitabine/cisplatin; intermediate: docetaxel/cisplatin; high: docetaxel alone). In addition, Abraxas and RAP80 mRNA expression were examined in 60/78 patients without mut. In the multivariate analysis of survival, BRCA1 expression emerged as a significant prognostic marker [Hazard ratio (HR) for patients with intermediate levels 4.8 ($P=0.02$); HR for patients with high levels, 13.4 ($P=0.004$)].
- E. Jassem presented results of a study that included 30 women with lung adenocarcinoma (mean age: 61 years), 15 of whom were never-smokers (WHO criteria) and 15 current or past smokers (mean 47.9 pack-years). All patients underwent curative pulmonary resection. Quantitative real-time-polymerase chain reaction (qRT-PCR) analysis was performed on mRNA derived from snap frozen tumor specimens. In univariate analysis three genes were particularly over-expressed in tumors of non-smokers: RRAD ($P=0.03$), transforming growth factor (TGF)-beta receptor-2 (TGFBR2; $P=0.02$) and progesterone receptor (Pgr; $P=0.02$). After correction for the impact of sex, histopathology, stage of disease, and multiple comparisons, RRAD and TGFBR2 were independently correlated with smoking history.

- J. Vansteenkiste presented updated results of a phase II randomized trial evaluating the administration of MAGE-A3 recombinant protein combined with immunological Adjuvant System AS02B as adjuvant treatment for completely resected stage IB or II MAGE-A3 (+) NSCLC. Patients were randomly assigned to postoperative MAGE-A3 or placebo (2:1) with immunizations q 3 weeks x 5, followed by q 3 months x 8. 182 patients were randomized: median age 63; 65% SCC. After a median follow-up of 44 months, 69 recurrences and 57 deaths were recorded. Group comparisons of disease-free interval (DFI), disease-free survival (DFS) and overall survival OS gave a HR of 0.75 ($P=0.127$), 0.76 and 0.81 respectively in favor of the MAGE-A3 group. Treatment was well tolerated, with excellent protocol compliance. 8% of the patients showed a baseline anti-MAGE-A3 antibody response. Induction of anti-MAGE-A3 IgG antibody response was observed in >98% of the patients immunized with MAGE-A3. No correlation of immune response and clinical outcome was observed.
- J. P. van Meerbeek reported an unplanned exploratory analysis of LU22-NVALT 2-EORTC 08012, which primarily did not show the expected survival benefit with neo-adjuvant chemotherapy in early stage NSCLC. From data available on 519 patients, only stage IA showed a HR suggestive of a significant deleterious effect.
- G. Scagliotti reported results of a study on 926 IIIB/IV NSCLC patients randomized to treatment with carboplatin-paclitaxel combined with sorafenib (400 mg) or placebo. Daily sorafenib or placebo was continued as maintenance therapy following up to 6 cycles of chemotherapy. Based on this planned interim analysis, there was no clinical benefit in terms of OS (10.7 vs. 10.6 months) by addition of sorafenib and independent monitoring committee stopped the trial. Patients in sorafenib group with squamous NSCLC had a greater mortality; causes of death were progression of disease (28.8%), other (5.0%), unknown (2.3%), study treatment toxicity (1.8%) and respiratory failure (0.9%). Fatal pulmonary hemorrhage was reported in 13 patients (1.4%) overall, with 9 events in the squamous cell subset.
- J. von Pawel presented results of a study in 73 patients, stage IIIB/IV patients, ECOG score 0–2, who were, after failure with first-line or second-line chemotherapy, randomly assigned to 250 mg bid ($n=36$) or 150 mg bid ($n=37$) of BIBF 1120 - a novel, oral, potent angiokinase inhibitor blocking the vascular endothelial growth factor receptor (VEGFR) 1/2, fibroblastic growth factor receptor (FGFR) 1/3 and platelet-derived growth factor receptor (PDGFR) α/β tyrosine kinases. Pharmacokinetic (PK) information was available in 71 patients (736 plasma samples). The median PFS of all patients ($n=73$) was 1.6 months and the stable disease rate was 48% without a significant difference between both treatment arms. Patients with an ECOG score of 0–1 ($n=57$) had a median PFS of 2.9 months without any difference between both treatment arms. The stable disease rate was 59%. The median OS of all patients was 22 weeks (ECOG 0–2) and 38 weeks in patients with ECOG performance status 0 or 1. The most frequent adverse events were grade 1 or 2 and included nausea, diarrhea, vomiting, anorexia and fatigue.
- A. Vergnenègre showed that the elderly are a heterogeneous population. The current challenge is to modify the inclusion criteria, with a validated comprehensive geriatric assessment (CGA) and test and validate this tool for advanced NSCLC in a phase III trial (ESSOGIA, GFPC 08-02) with patient selection on the basis of performance status (PS) and age (arm A: ≥ 70 years, PS 0, 1, 2 one drug treatment; >75 years and or PS2, ≤ 75 years and or PS 0 or 1 two drugs with platinum) or CGA (arm B: for frail best supportive care, dependent one drug and for independent two drugs with platinum). With an increase of 30% in time to treatment failure (toxicity, adverse event, progression, death), the number of needed subjects is 229 by arm.
- Y. Lievens retrospectively retrieved CT scans of 35 locally advanced (LA) NSCLC patients with pathologically proven mediastinal involvement. Involved nodal areas were redefined on CT and PET by visual correlation, target definition was restricted to PET-positive regions. Prescribed dose (PD) was 66Gy/2Gy except in case of endpoint (EP) violation. Primary EP was tumor coverage. Secondary EP were doses to the spinal cord, lung and heart. For esophagus tolerance, $D_{\max} < 66$ Gy and $D_{2\text{cm}^3} \leq 60$ Gy were defined. The study showed that intensity-modulated radiotherapy (IMRT) has the potential to significantly increase PD compared with 3D-CRT if the esophagus is not considered a limiting organ at risk (OAR). If it is, the advantage is lost.
- J. R. Pantarotto reported a study in locally advanced lung cancer patients eligible for concurrent CT-RT and RGRT delivery who underwent a repeat 4DCT planning scan after 15 fractions. Of the first 12 patients analyzed, 7 had a reduction in primary target volume (PTV) after 15 fractions, with reductions exceeding 20% in 2 patients. Of the 5 remaining patients, 4 had stable disease and only 1 experienced an increase in PTV. These preliminary results suggest that 'adaptive radiotherapy' has a limited role when RGRT is used to reduce toxicity.

- J. B. Adkison reported a study in 46 patients judged not to be surgical candidates with stage I-IV NSCLC who were enrolled for definitive radiotherapy delivered via helical tomotherapy and limited to the primary site and clinically proven or suspicious nodal regions without elective nodal irradiation. No grade 3 acute pneumonitis or esophageal toxicities were observed. Pneumonitis rates were 70% grade 1, and 13% grade 2. Multivariate analysis only identified lung normalized tissue dose (NTD)_{mean} ($P=0.012$) and administration of adjuvant chemotherapy following radiotherapy ($P=0.015$) to be independent risk factors for grade 2 pneumonitis. Only 7 patients (15%) required narcotic analgesia for esophagitis, with only 2.3% average weight loss during treatment. Best in-field response rates were 17% complete response with 43% partial response. The median survival was 18 months.
- R. Timmerman reported results of a protocol that utilized stereotactic body radiotherapy (SBRT) with ablative prescription dose. The study accrued a total of 59 patient with T1 or T2 tumors. The criteria for early stopping due to toxicity was not met in each of three interim toxicity assessments. With median follow-up of 14.7 months, there was one (2%) grade 4 and 7 (13%) grade 3 protocol-defined pulmonary/upper respiratory adverse events reported as related to treatment. Patients continue to be followed for the primary endpoint of 2-year local control.
- M. Van Zwielen presented a study of 114 lung cancer patients treated with conventional RT with a dose of 45 Gy to 88 Gy over 5-6 weeks. Tumor stage ranged from T1N0 to T4N3. Patients received repetitive cone-beam computed tomography (CBCT) scans for an off-line setup correction protocol. Forty-seven patients (41%) manifested considerable anatomical changes. Tumor regression was observed in 37 patients (32%), while only one patient (1%) showed tumor progression during therapy. Changes in atelectasis were found for 26 patients (23%), in 20 dissolving (18%) and in 6 increasing (5%), pleural effusion in 13 patients (11%).

Conclusion

It is a critical moment in lung cancer, both in disease prevention and disease management. Pharmacogenomic research is advancing at a great pace and novel findings are coming to light. New approaches in early detection and multidisciplinary approaches are being discovered. Radiation oncology is experiencing a technological revolution. Molecular biology has surfaced as a key to understanding cancers. In addition, the tremendous amount of information now electronically available has had a great impact on everyday practice.

All of these advances invite sober reflection on key questions. What hurdles must the medical oncologist, radiation oncologist, surgeon and pulmonologist overcome in daily practice and in clinical trials – not to mention those faced by radiologists, pathologists and others involved in the management of lung cancer patients? We have a unique opportunity to use modern technological advances to capture the overwhelming data reported in the literature, and to apply these findings almost immediately to our translational research.

We are now in a position to offer personalized patient assessment and care. It's time to take the crucial step.

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