

REPORT PERSPECTIVES IN LUNG CANCER 2009 BRUSSELS

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Introduction

Perspectives in Lung Cancer is an educational meeting in the field of Respiratory Oncology. It had its celebration 10th edition in Brussels on March 6-7, 2009. The aim of this congress is to provide a concise overview of the new data of the last year. This edition was attended by approximately 750 participants.

Session I: Diagnosis and staging

The 7th edition of TNM classification of non-small cell lung cancer (NSCLC) was presented. This new NSCLC classification – based on survival data of 67,725 patients (1990-2000) – is more accurate to predict outcome of different patient groups based on stage. Changes are in the Tumour (T) and Metastasis (M) descriptors, while there is no change in the N descriptors ¹. An overview is provided in Figure 1.

Stage is one of the major determinants of outcome of NSCLC. Optimal staging depends on the accuracy and availability of different non-invasive and invasive techniques. In addition to computed tomography (CT) scan of the chest including the upper abdomen, performing positron emission tomography with ¹⁸F-fluoro-deoxy-glucose (FDG-PET) in the initial staging provides additional information especially on mediastinal and extrathoracic lesions. Esophageal (EUS) or endobronchial ultrasound (EBUS) guided aspiration nowadays permits mapping of mediastinal lymph node spread ². Patients with clinical IB-IIIB lung cancer with mediastinal node enlargement (discrete or extensive) and intent of curative treatment should undergo PET scan. In patients with peripheral stage I tumours, negative mediastinal findings of PET allow to omit invasive confirmation of the lymph node status before surgery. PET is also used in reassessment after induction treatment in IIIA-N2 NSCLC and provides information on both lymph node downstaging as well as primary tumour response.

With all these excellent staging tools at hand, there is growing evidence to adapt staging sequences to performance of CT, PET and E(B)US at baseline, and using a first mediastinoscopy and a PET-CT scan for restaging after induction treatment ³.

In recent years, fine needle aspiration (FNA) cytology also became more important in the diagnosis of malignancy. These techniques often result in small samples, which is a challenge in an era where there is an increasing importance of biomarkers such as tumour histology subtype and others for treatment choices.

Session II: Surgery

Use of low dose CT scan for lung cancer screening led to an important increase in the number of detected lung nodules. It was reported that an approach of these nodules with video-assisted thoracic surgery (VATS) was as accurate but less debilitating than muscle sparing thoracotomy. Randomised studies will address the critical issue if low dose CT screening indeed reduces lung cancer related mortality ⁴.

Surgery is the treatment option of choice in stages I-II, and adjuvant chemotherapy became standard treatment for stage II and probably for some patients with stage IB, with an expected 5-year survival

benefit of about 5%. To improve this benefit, ongoing research focuses on better selection of patients who will benefit of adjuvant chemotherapy, and on better predictive factors to choose one therapy or another. Evidence is growing that gene signatures may predict survival. Different studies with customized adjuvant chemotherapy are launched, with several biomarkers of interest, such as BRCA-1, ERCC1, and others.

In stage IIIA, single modality treatment with surgery or radiotherapy is not optimal. Treatment should be a multidisciplinary combination of systemic (mainly chemotherapy) and local (surgery or radiotherapy) treatment. Best prognosis after resection is seen in patients with mediastinal downstaging after induction chemotherapy and who can be offered a complete resection by performing a lobectomy⁵. If stage IIIA is due to unexpected N2 disease, adjuvant chemotherapy should be given, while the role of adjuvant radiotherapy remains unclear.

In selected T4 patients without mediastinal lymph node involvement, induction chemoradiotherapy followed by surgery can be rewarding if a complete resection can be obtained.

Session III: Radiotherapy

Concurrent chemoradiotherapy is the preferred approach in case of unresectable stage III NSCLC, but we should realise that quite some patients are not fit enough to receive this approach⁶. The benefit of adding induction versus consolidation chemotherapy to the concurrent treatment is unproven and further studied, as is the role of maintenance chemotherapy after chemoradiotherapy. The effect of increasing the radiation dose to improve survival is evaluated, as the evolution to more precise radiation techniques permits to deliver higher total doses without unacceptable toxicity.

In medically inoperable patients with stage I disease, stereotactic radiotherapy could be a better alternative than standard radiotherapy.

Session IV: Pulmonary neuro-endocrine lung tumours (NET)

The pathological spectrum of neuro-endocrine lung tumours varies from typical carcinoids to small cell lung cancer (SCLC). The intermediate entities of atypical carcinoids and large cell neuro-endocrine carcinomas often make the pathologic diagnosis challenging. Correct classification, based on morphology and immunohistochemistry is important however, as survival is clearly related to the type of NET⁷.

Patients with a bronchial carcinoid tumour should be offered surgery whenever possible. In case of inoperability or distant metastasis, data on therapeutic options are limited, and these include biotherapy or chemotherapy. The results of therapy with radiolabelled somatostatin analogues in patients with a positive octreotide scan are promising.

For true SCLC, chemotherapy based on platinum and etoposide remains the preferred first line option. The evidence in favour of clinical benefit of second line chemotherapy in patients with relapsed SCLC remains limited. In case of relapse three or more months after having completed first line treatment, patients may benefit from re-treatment with the same regimen. Oral or intravenous topotecan is another valid second-line option, superior to best supportive care in overall survival (25.9 vs. 13.9 weeks, HR 0.64, 95% CI 0.45-0.90) and in symptom control⁸. Trials evaluating the place of amrubicin (a new anthracycline compound) and targeted therapies are ongoing.

Session V: Supportive care

Pleural effusions causing 'wet' stage T4 are associated with a worse prognosis than other T4 lung tumours. In fit patients, thoroscopic talc poudrage remains the preferred approach to obtain durable relief of symptoms. The effect of cytokines to influence pleural effusion formation is under investigation.

Bone metastasis is another frequent problem in patients with lung cancer. The administration of zoledronic acid significantly reduces the incidence of skeletal related events ⁹. Evidence for an additional positive effect of this treatment on disease recurrence and survival is growing, based on data of three studies performed in breast cancer patients.

Chemotherapy-induced anaemia can effectively be treated with erythropoietic substitution agents resulting in decrease of red blood cell transfusions and improvement of quality of life. It became clear that treatment of anaemic patients not receiving chemotherapy or targeting high haemoglobin levels to prevent anaemia may result in worse outcome. Therefore, it is important to treat patients based on existing guidelines; when doing so, there is no evidence for negative impact on survival ¹⁰.

Interventional bronchoscopy with laser therapy and stent placement is mostly associated with bulky disease for symptom control. It also gained attention, e.g. with autofluorescence bronchoscopy, in the radical treatment of early lung cancer lesions in central airways.

Session VI: Advanced NSCLC

A large phase III trial recently showed that treatment of advanced NSCLC with cisplatin-pemetrexed resulted in non-inferior overall survival compared to cisplatin-gemcitabine. Moreover, there was a statistically significantly better overall survival for patients with adenocarcinoma or large cell carcinoma when treated with cisplatin-pemetrexed ¹¹. The reverse was true for patients with squamous cell carcinoma. A major advantage of pemetrexed is its mild toxicity profile for a chemotherapeutic agent.

In a selected group of patients (non-squamous histology, no major cardiovascular problems, no haemoptysis), addition of bevacizumab (an anti vascular endothelial growth factor antibody) to cisplatin-gemcitabine provided modest benefit in progression-free survival, without difference in overall survival ¹².

The other recent advance is cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR). In the large phase III FLEX study, the combination of cetuximab and cisplatin-vinorelbine resulted in significantly better overall survival compared to chemotherapy alone in patients with EGFR expressing advanced NSCLC. This benefit was independent of histology ¹³.

Session VII: Biomarkers

Gender, histology, smoking history and ethnicity are known clinical predictive factors for response to EGFR tyrosine kinase inhibitors (TKIs). EGFR activating mutations and EGFR high gene copy number or amplification as assessed by fluorescence in situ hybridisation are the biomarkers of interest. Ongoing research is elucidating the prognostic and predictive value of these biomarkers, and how they may guide optimal treatment for NSCLC with EGFR-TKIs.

Session VIII: Mesothelioma

Patients with advanced mesothelioma should receive a combination of platinum and pemetrexed, which can also be considered in case of sensitive relapse (i.e. at least 3 months after the end of 1st line therapy). Palliative radiotherapy has its indication in pain relief in case of chest wall infiltration. Selected early stage patients can be considered for radical multi-modality treatment in dedicated centres or clinical trials. In this setting, induction chemotherapy followed by extrapleural pneumonectomy is associated with better survival outcomes than upfront surgery followed by adjuvant therapy. The role of adjuvant radiotherapy is not defined yet. In regard to multimodality treatment, it should be noted that an important number of the patients initially considered for this approach, are not able to complete the whole therapy.

As the overall improvement in outcome of mesothelioma patients remains very modest, a better understanding of the biology of the disease and of biomarkers is warranted.

Figure : Descriptors, proposed T and M categories, and proposed stage groupings for the 7th TNM edition ¹

Sixth Edition T/M Descriptor	Proposed T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5–7 cm)	T2b	IIA	IIIB	IIIA	IIIB
T2 (>7 cm)	T3	IIIB	IIIA	IIIA	IIIB
T3 invasion		IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the sixth edition for a particular TNM category.

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