

sensitivity and specificity of 69% and 71% of CT scan and 45% and 65% of MRI respectively does not provide sufficient informations for these patients. Modern techniques as positron emission tomography (FDG-PET or FDG-PET/CT) and endobronchial (EBUS) or endoscopic (EUS) ultrasound guided fine-needle aspiration (FNA) have also been used for mediastinal staging. In a prospective study with 202 patients found Gonzalez-Strawinski and al. that current FDG-PET technology alone does not appear to be sufficient to warrant reliable treatment changes or the avoidance of mediastinoscopy in the evaluation of patients with NSCLC. FDG-PET results have been shown to be difficult to interpret after radiotherapy and the best time to repeat it still remains unproved. An inherent problem of the FDG contrast is that inflamed tissue will absorb it, so that granulomatous or inflammatory mediastinal disease or cases of obstructive malignant processes resulted to difficulty identifying mediastinal malignancy with FDG-PET. In our series we found that patients after induction chemoradiotherapy showed a strongly FDG accumulation due to inflammatory reaction of radiated mediastinal tissue, so that the number of false positive cases ranged by 20%. Hellwig et al reported about the high negative predictive value in mediastinal restaging of FDG-PET so that only low values of lowstandardized uptakes allows for omission of RM .

EBUS and EUS guided FNA are promising technique for staging of solid lesions and lymph nodes located adjacent to the trachea, the main bronchi and the esophagus but is not comparable to mediastinoscopy or RM . Selection of the patients for EUS or EBUS-FNA was based on computed tomographic scanning and with that only in patients with pathological radiological findings. Both techniques are used to assess the entire mediastinum or to stage predominantly only one nodal station, but they are not used for the systematical standardized exploration of individual nodes as performed by mediastinoscopy. Moreover, the echogenic characteristics alone of a node might not be as reliable after radiation as they are before. In our experience representative material from scarred and fibrotic lymph nodes after chemoradiotherapy is difficult to be taken, the number of false positive results in the cytologic examination of FNA should be not underestimated. Particularly for local advanced disease and neoadjuvant treatment a histological tissue diagnosis must still be obtained, so that it is unlikely that the addition of transtracheal, transbronchial, and endoscopic ultrasonographically guided FNA will sufficiently rule out disease relative to the histologic results achieved from mediastinoscopy. EBUS and EUS are supplementary diagnostical tools and may contribute to improve staging, especially in cases with metastasis in the hilar nodes or the mediastinal nodes which could not be reached by CM or RM.

Some investigators have focused on an early intensification of preoperative downstaging by bimodality induction including chemotherapy as well as radiation therapy before surgery. In these patients the clinical classification especially the mediastinal staging after the induction treatment must yield the possible maximal accuracy. Bueno et al and Voltolini et al pointed out in two separate reports that nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Downstaged patients to N0 status survived 59% at 3 years and 35.8% at 5 years respectively. However as have been proved the persistence of lymph node involvement after induction treatment has a discouraging prognosis with 3 years survival of 0% in the first and 5 years survival of 9% in the second study. This data support surgical resection only for downstaged patients and that a direct effort should be made to improve the accuracy of restaging before resection. Because of this, our oncological group considered to performe the RM in order to re-evaluate the mediastinum taken biopsies and verifying the nodal

status in all patients entered into two complete phase II and one phase III trial and selecting patients for resection. Technical aspects of RM are well described in previous reports. The presence of peritracheal adhesions makes the exploration more complex than by the initial mediastinoscopy. Analogous to other reports we didn't have a perioperative or postoperative mortality. A low rate of morbidity was observed (4.2 %) concient with reported results from other series. Furthermore additional operations due to intraoperative complications were not necessary. The incidence of recurrent nerve palsy was in accordance with the numbers after first mediastinoscopy.

We conclude that RM is a feasible and safe surgical procedure for restaging of patients with primary locally advanced, recurrent or second primary lung cancer. There are no mortality, the perioperative complications rate are very low. In patients after induction treatment RM proved to be less sensitive than the first procedure because of adhesions and fibrotic tissue. Because of the higher sensitivity, specificity and accuracy in compare to radiological investigations, FDG-PET and ultrasound guided FNA remains RM despite the technical complexity the criterion standard for mediastinal restaging in patients with local advanced lung cancer and induction treatment.

## Session E05: IASLC Staging Project

E05-01

IASLC Staging Project, Mon, Sept 3, 16:00 – 17:30

### The IASLC lung cancer staging project

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The History: Peter Goldstraw.

The Tumour, Node, Metastases (TNM) system for the classification of malignant tumours was developed by Pierre Denoix in a series of papers between 1943 and 1952 (1;2). In 1953 it was accepted by the International Union Against Cancer (UICC) Committee on Tumour Nomenclature and Statistics. In 1968 it appeared in the 1st edition of their Classification of Malignant Tumours. In 1973 the American Joint Committee on Cancer (AJCC) Task Force on Lung Cancer accepted the recommendations of Drs. Mountain, Carr and Anderson for a clinical staging system of lung cancer (3). The following year the UICC accepted these proposals, unifying the 2 staging systems, in their 2nd edition of the TNM Classification of Malignant Tumours.

The AJCC recommendations were based upon a database which consisted of 1,712 cases of non-small cell lung cancer (NSCLC) diagnosed at least 4 years before the analysis of results. Nearly all of the descriptors used today in staging lung cancer were established in that relatively small database, including the only size cut off for T descriptors (that of 3 cms which distinguishes T1 from T2 tumours), the impact of specific areas of local invasion (visceral pleura, diaphragm, chest wall and the mediastinum and its contents), the proximal bronchoscopic extent of disease, pleural effusion and the extent of atelectasis or pneumonitis. In this version the highest "T" descriptor was 3, that for "N" was 2 and the highest stage was stage III.

Since that pioneering work there have been 4 more revisions. The size of the database on which these changes were made has increased, to 5319 in the 5th revision (4), the review process has become progressively more "International" and a few new descriptors have been added, resulting in the expansion of the "T" category to 4, the "N" category

to 3 and the number of stages to IV. However, the database remained predominately based upon a surgical series from one centre in the USA. With the retirement of Dr. Clifton Mountain the International Association for the Study of Lung Cancer (IASLC) felt there was a need to continue his work and an opportunity for it, as the only global body to include specialists in all of the fields of diagnosis, treatment and research into lung cancer, to create an International database of cases treated by all modalities of care worldwide. With finances provided through a restricted educational grant by Eli Lilly and Company, data transfer, collection and analysis by Cancer Research And Biostatistics (CRAB) and the generous support of 46 databases in over 19 countries we have amassed data on over 100,000 cases of lung cancer treated between 1990 and 2000 (5). At a later stage, additional funding was obtained through a competitive process within the AJCC. An initial sift excluded those cases with inadequate data on staging or survival, those in which cell-type was unclear or inappropriate, those with recurrent disease rather than a new primary cancer and those outside our intended study period. There remained 81,021 cases suitable for further analysis, consisting of 13,290 cases of small-cell lung cancer (SCLC) and 67,731 cases of non-small cell lung cancer (NSCLC). This data came from clinical trials, tumour registries, International registries, surgical registries, series treated by surgery and other modalities and consortia. All modalities of care were represented but understandably the largest proportion were treated by surgery (41%) followed by chemotherapy (23%) and radiotherapy (11%), the rest being treated by combined modality care or best supportive care. European centres contributed 58% of the NSCLC cases followed by North America (21%), Asia (14%) and Australia (7%). In the NSCLC cases 53,646 had data on clinical staging. There were 33,933 with pathological staging data and in 20,006 there was data on both cTNM and pTNM.

The analysis of this data was completed at the end of 2006 and the subsequent recommendations for the 7th edition of the TNM Classification were submitted to the UICC in December 2006. The recommendations, with supplementary suggestions regarding the TNM staging of SCLC and carcinoid tumours, a new concept in nodal classification and comments on the role of additional prognostic factors will be submitted to the AJCC in June 2007. These recommendations will be published in the Journal of Thoracic Oncology in a series of discussion papers commencing in July 2007 and will form the basis of the subsequent talks in this session. We have already started to prepare for the next phase of the project which will extend the retrospective database and create a prospective database for future revisions. This will enable us to look further into some issues that could not be addressed in a retrospective fashion.

Our recommendations are now subject to the internal review processes of the UICC and AJCC, which include review by National cancer committees and an International panel of experts. Once these discussions are complete the 7th edition will be published in January 2009.

#### Reference List

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- (5) Goldstraw P, Crowley J, et al. The IASLC International Staging Project on Lung Cancer. Journal of Thoracic Oncology 1, 281-286. 2006.

E05-02

IASLC Staging Project, Mon, Sept 3, 16:00 – 17:30

#### IASLC Staging Project: T-descriptors

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#### Introduction

In 1999 the International Association for the Study of Lung Cancer (IASLC) initiated an international staging project with the objective to analyse a large international database of patients with lung cancer in order to study the T, the N and the M components of the current lung cancer classification and staging system, and eventually recommend revisions to the present edition (6th) of the TNM classification. If the resulting changes were accepted by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC), they would appear in the 7th edition of the TNM classification for lung cancer, due to be published in 2009 (1).

This paper is presented by the T-descriptors Subcommittee on behalf of the International Staging Committee, Cancer Research and Biostatistics, Observers to the Committee, and Participating Institutions.

#### Material and method

Data on 100,869 patients were collected in the international database and analysed by Cancer Research and Biostatistics (CRAB). The T-descriptors subcommittee and CRAB analysed a subset of 18,198 patients with non-small cell lung cancer (NSCLC) who had a complete set of cTNM or pTNM and sufficient T-descriptor details to support the assigned T-stage. These included 180 patients with M1 tumours with additional nodule(s) in a different ipsilateral lobe from the primary tumour lobe. In the populations of patients with complete cTNM0 and pTNM0, 5,760 and 15,234, respectively, had sufficient information on T-descriptors. Too few patients had specific information on descriptors of higher Ts, and most T2 descriptors (except for tumour size) and all T3 and T4 descriptors (except for additional nodule(s)) could not be analysed. The present study is focussed, therefore, on tumour size and additional nodule(s) in the tumour-bearing lobe or different ipsilateral lobe. For the specific analysis of tumour size, the population of patients with pT1-2N0M0 completely resected (R0) tumours was selected, but the identified cutpoints were also explored in the population of patients with any N tumours and incomplete resections. This larger population of patients was also used to analyse the tumours with additional nodule(s) and their relations to T3, T4 and M1 tumours. A learning set of approximately 2/3 (4,891 patients) was used to develop the optimal size cutpoints that were then tested in the validation set of the remaining 1/3 (2,589 patients). In the derivation of tumour size cutpoints, the running log-rank statistic produced by each hypothetical cutpoint in the pN0M0R0 learning set was graphed against tumour size, and the tumour size which coincided with the highest log-rank statistic was chosen as the optimal cutpoint, after rounding to the nearest whole cm. The results were internally validated by geographic region and type of database, and externally validated using the Surveillance, Epidemiology and End Results (SEER) registry (2).