Vansteenkiste Johan (Catholic University Leuven, 1996): ***Staging and treatment of non-small cell lung cancer with ipsilateral mediastinal lymph node metastases: A clinical and literature study.***

Summary
Non-small cell lung cancer is the most frequent fatal malignant disease. For patients in the early stages, resection is the treatment of choice. About one third of the patients with NSCLC, however, have locally advanced tumours, among others those with N2-disease. The optimal management of this group with marginal resectability remains a difficult challenge for the treating clinician. Even a small progress in the therapeutic results of this so frequent disease would save many lives per year. From this thesis, based on an extensive literature study and on our own clinical data, we draw the following conclusions:

In the first chapter, the literature data on **survival of surgically explored patients with N2-NSCLC** were studied. Despite sometimes appealing reports, the finding of N2-disease stands for a very poor prognosis: in the total group of those patients, the 5-year survival was at best 5%. The in the literature frequently reported 5-year survival results of 30% came from a very selected subgroup of these patients; they accounted for very limited numbers, even in large cancer centres. These selected patients were those with a clinical N0-1-stage (i.e. no preoperative evidence of N2-disease, cN0-1), undergoing a complete resection. Despite apparent major differences in the reported survival rates in the literature, the overall prognosis of those cN0-1 patients found to have N2-disease at pathological examination of the resection specimen (i.e. postoperative pathological N2, pN2), appeared to be similar in all continents and varied between 15 and 25% 5-year survival rate. The subgroup of patients with left upper lobe tumours and a cN0-1 status after a negative mediastinoscopy had a more favourable prognosis. Surgical exploration of clinical N2-patients (i.e. preoperatively known N2-disease, cN2) was rarely reported in Europe. In series from other continents, the 5-year survival rates in this group seemed to be at best 5 to 10%, with figures as low as 2% in experienced centres using clinical features, standard chest X-ray, and bronchoscopy in the preoperative staging. This percentage of survival was very near or even inferior to the risk of perioperative mortality. Incomplete resections did not contribute to 5-year survival. The best strategy to avoid these incomplete resections seemed to be the use of a preoperative mediastinoscopy.

In chapter 2, the **prognostic factors determining the survival** in literature series of surgically explored patients with N2-NSCLC were examined. The analysis of these prognostic factors in a single paper was usually hampered by the limited number of patients. Although methodological differences between centres must be kept in mind, as well as the fact that all events are multifactorial, the good agreement between centres in the used definitions of prognostic factors, permitted to draw some conclusions from pooled data. There was a very large evidence and general agreement in the literature that N2-patients with a less advanced primary tumour (T-stage) have a better prognosis. This was the case for all operable T-stages (T1 versus T2, T1 versus T3, T2 versus T3). There was evidence that a squamous cell type is a favourable prognostic factor. The same was true for patients who have only one metastatic mediastinal lymph node level. There was some evidence that the presence of extracapsular spread in metastatic mediastinal lymph nodes is an unfavourable prognostic sign. Many authors considered this situation inoperable, since complete resection was often not possible. It was not clear if patients with metastatic lymph nodes in the lower mediastinal levels only, have a better prognosis than those with metastases in the higher levels only. The subcarinal mediastinal lymph nodes were a notable exception. There was ample evidence that patients with lymphatic metastases in this site have a worse prognosis. It was not clear if there is a difference in the prognosis of patients undergoing lobectomy versus those undergoing pneumonectomy. Treatment failure in N2-patients treated with surgery and postoperative irradiation was mainly due to distant metastases, especially in the brain.

In chapter 3, our **analysis of 140 patients with N2-NSCLC undergoing resection** was reported. Combined with the literature experience, and with the advantages of a multivariate analysis, we found that the chances for cure of pN2-patients undergoing surgical treatment depended on: *1. The staging and the type of treatment*: the expected 15 to 25% 5-year survival came from patients with a preoperative cN0-1 stage undergoing complete resection. In our multivariate model of pN2-patients the relative risk for cN2 was 1.43. In cN2-patients, except those with strictly minimal N2 at mediastinoscopy, the 5-year survival rate was very poor and nearly equal to the postoperative mortality. Direct surgical exploration is thus not worthwhile in these cases; *2. A clinical characteristic*: the performance status of the patients determined the survival, with a relative risk of 1.37 for individuals with a more than 0 score on the WHO performance scale; *3. Tumour characteristics* : the extent and the pathology of the primary tumour had an influence on the prognosis, with practically no chances of survival for patients with T3N2 or T4N2 tumours, and a relative risk of 1.29 for non-squamous histology in our model; *4. Lymph nodes characteristics* : the number of metastatic mediastinal lymph node levels was important, with a worse prognosis (relative risk 1.68) for patients with more than one metastatic level. The topography of these nodes was less important, except for metastases in the subcarinal region, which aggravated the prognosis;

5. Biological characteristics : survival was unlikely when lactic dehydrogenase or carcinoembryonic antigen were elevated at diagnosis.

In chapter 4, the **role of bronchoscopy with transcarinal needle aspiration biopsy**, in the staging of NSCLC was examined. With this technique, adequate samples of the subcarinal mediastinal lymph nodes were obtained in 90% of the patients selected by CT scan. The sensitivity of detecting malignant subcarinal mediastinal lymph nodes was 79%. The technique was complementary to mediastinoscopy to obtain pathological evaluation of N2-disease. In patients with enlarged mediastinal lymph nodes in the posterior subcarinal region (thought to be difficult to reach by mediastinoscopy by the attending thoracic surgeon), an adequate specimen for staging could be obtained. The use of a large diameter Schiessle-needle through a rigid bronchoscope allowed the application of strict pathological quality criteria, precluding false positives. The procedure was more likely to be successful when enlarged subcarinal mediastinal lymph nodes were present on CT-scan, and in case of a more advanced T-stage. Significantly more metastatic subcarinal mediastinal lymph nodes were found in patients with a more advanced T-stage, a non-squamous tumour, or in case of an abnormal endoscopic appearance of the carina. A trend in this direction was seen for endoscopically visible tumours or right-sided tumours. We concluded that transcarinal needle aspiration biopsy and mediastinoscopy were complementary to each other, and that there is still a place for this endoscopic staging technique in the current period of induction treatment.

In chapter 5, the **role of induction treatment in N2-NSCLC** was studied. Although a very promising approach, most of the findings on induction treatment in stage IIIA-N2 NSCLC came from phase II feasibility trials or very small randomised reports. Our extensive literature study learned us the following: 1. treatments with low-dose cisplatinum seemed to be less effective; 2. the pulmonary toxicity of mitomycin-C was a matter of concern; 3. there was no clear superiority of chemoradiation induction over chemotherapy only in terms of response or resection, on the condition that a (preferably 3-drug) high-dose cisplatinum regimen was used; 4. the toxicity of chemoradiation induction seemed to be somewhat higher, both during induction (mainly due to neutropenic infection and radiation pneumonitis) and in terms of postoperative morbidity/mortality (mainly due to respiratory insufficiency and fistula formation); 5. the first long-term data indicated that good chances for survival were mainly found in patients with a pathological complete response, which was almost exclusively found after a major clinical response.
We found that the VIP regimen (adding ifosfamide to the more classical cisplatinum-vindesine combination) was an effective 3-drug regimen in good performance patients with advanced stage III or stage IV NSCLC. Its activity, together with its manageable toxicity - without severe renal or pulmonary toxicity - makes it an attractive candidate for induction treatment. This finding was confirmed by our preliminary data on VIP as induction treatment. A high response rate and the possibility for downstaging and pathological complete response were found.

General conclusion and perspectives: The staging of NSCLC patients should preferably include mediastinoscopy. The good results of mediastinal staging with positron emission tomography with ^{18}F-fluoro-2-deoxyglucose might change this option in the future.
Direct resection is the best strategy when mediastinoscopy shows either absence of metastasis or only minimal metastasis in the ipsilateral mediastinal lymph nodes. In this group survival is worthwhile, but systemic recurrence remains the main obstacle for cure. Postoperative chemotherapy showed some promising findings, but large randomised confirmatory trials are at yet only at the beginning of recruitment.
In patients with preoperatively known non-minimal N2-disease, direct resection is not worthwhile. Induction treatment with chemotherapy, with or without thoracic radiotherapy, is actually the most promising approach. It can yet by no means be considered as a clinical standard. There is a place for it, however, in large-scale randomised trials, looking for an answer on various still open questions, among others whether induction therapy really works and improves long-term survival, or whether a local treatment incorporating surgery is superior to a non-surgical approach with chemoradiation therapy.
It will be mandatory to stratify for prognostic factors in these future randomised trials. The lack of this stratification can be a cause for the numerous unclear answers and contradictions in the currently available data.
Further priorities in the future will be the search for more active chemotherapy schedules, for agents active in the central nervous system (one of the major relapse sites in the current combined modality treatments), and also for the clinical role of biological or genetic therapies.
Although many questions are still open, we believe that the chances for NSCLC patients with N2-disease will ultimately be improved by further clinical research on and refinement of our actual systemic therapy in a well designed combined modality treatment.