Rationale: 1994, selected patients early stage IIIA-NSCLC (operable, 1-2 LN involved at mediastinoscopy, no clinical N2, no bulky/extranodal disease) were taken to upfront surgery (S) at centers in Europe/North America. We compared this approach to aggressive tri-modality therapy - induction chemotherapy (CTx), preoperative radiochemotherapy (RTx/CTx) and definitive S - in a multicenter randomized GERMAN KREBSHILFE trial (full trials grant).

Patients and Methods: Operable IIIA pts (criteria above, mediastinoscopy, central T3N0-1, WHO 0,1) stratified (TN-group, center) and randomized: arm A - S and postoperative RTx (50-60 Gy); arm B - induction CTx (3 x cisplatin (P) 60 mg/m2 d 1+7/etoposide (E) 150 mg/m2 d 3,4,5) + concurrent RTx/CTx (45 Gy; 1.5 Gy bid; 1 x P 50 mg/m2 d 2 + 9, E 100 mg/m2 d 4.5,6) + S (prophylactic cranial irradiation (PCI) in both arms (PCI vs no PCI). Data on brain-relapse-free surv are analyzed with different policy for insufficiencies, bleeding, embolisms, peri- and postoperative morbidity/mortality not significantly different does not allow valid conclusions concerning this endpoint. Currently, there are insufficient data to exclude all patients with persistent mediastinal disease from surgery. Assuming baseline endoscopic mediastinal staging in the near future, we explored a restaging strategy combining tissue analysis of mediastinal LNs obtained post-induction, and FDG-PET for monitoring response in the primary tumour.

Results: 1194 to 7011 122 pts randomized. 6 pts (3/arm) not eligible (missing status, pts refusal, early progression prior any study therapy). 108 pts eligible for complete analysis 3/2007: Pts characteristics M 90 F 16; age median (med) 59 (37-71); SCC 55 adeno-ca 35 LCC 16; A: n = 51 pts T3N0-1 3 T1-2N2 38 T3N2 10; B: n = 55 pts T3N0-1 1 T1-2N2 45 T3N2 7. A: S 50/50 probatory thoracotomy (PT) 5/50 R1/2 10/50 complete resection (R0) 35/50; B: S 39/54 PT 1/54 R1/2 6/54 R0 32/54; peri- and postoperative morbidity/mortality not significantly different between A/B (rate of early postoperative deaths, infections, stumps insufficiencies, bleeding, embolisms, postop duration of hospitalization, time on postop respirator, time on ICU). Strong trend for more limited surgical resections following induction: number of pneumonectomies: A 22, B 11. Although terminated early due to slow accrual/emerging data for adjuvant CTx (IALT), the survival (surv) results as follows: median (med) overall surv: A 15 mo vs B 29 mo (p = 0.15 Wilcoxon W); med event-free surv: 9 mo vs 15 mo (p = 0.12 W); med disease specific (spec) surv 10 mo vs 18 mo (p = 0.026 W). 5-year overall surv 18% vs 16%; event-free surv: 20% vs 24%; disease spec surv 23% vs 24%. Beyond 3 yrs from randomization intercurrent events (co-morbidities) and second cancers predominant reason for deaths. Med surv of pts still alive 3/07: 94 mo (n = 14, 73+149+).

Conclusion: This tri-modality protocol was feasible/ safe in the multicenter setting. Following complex bi-modality induction did not show increased morbidity/mortality. Strong trend towards lung-sparing surgery in the arm with preoperative complex induction (down-staging? organ-sparing effect?). Results of this trial mandate rate of less extensive S interventions (eg. lobectomies) as further important endpoint to be added within clinical trials of comparable pts populations (significant risk for pneumonecctomy at thoracotomy). Although surv data favoured tri-modality in the first four yrs - overall no of pts randomized does not allow valid conclusions concerning this endpoint. Currently, data on brain-relapse-free surv are analyzed with different policy for PCI in both arms (PCI vs no PCI).

A1-07 Combined Modality Therapy in NSCLC I, Mon, 13:45 - 15:30

Which patient is a candidate for surgery after induction treatment for stage IIIA-pN2 NSCLC? A prognostic stratification model based on morphometric-pathologic response in mediastinal nodes and primary tumour response on FDG-PET

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Background: Surgical resection in patients with stage IIIA-pN2 NSCLC is usually reserved for patients with downsstaging of mediastinal lymph nodes (LNs) after induction therapy. However, clinical restaging after induction therapy is often inaccurate. Moreover, there are insufficient data to exclude all patients with persistent mediastinal disease from surgery. Assuming baseline endoscopic mediastinal staging in the near future, we explored a restaging strategy combining tissue analysis of mediastinal LNs obtained post-induction, and FDG-PET for monitoring response in the primary tumour.

Methods: Baseline and repeat PET after three cycles of induction chemotherapy, as well as complete resection specimens of both mediastinal LNs and primary tumour, were available in 30 patients out of our prospective database of surgical multimodality therapy in IIIA-pN2 NSCLC patients (period: 04-1995 to 06-2002; ref. Lorent et al, Ann Oncol 15:1645, 2004). In these 30 patients, histological tumour grading of both LNs and primary tumour was performed by means of conventional morphometric procedures based on a point counting technique, as described by Gundersen (ref. Gundersen et al, APMIS 96:379, 1988). Three morphometric grading groups were considered: mediastinal downstaging (clearance of mediastinal disease), ‘minor’ residual mediastinal disease (<10% viable tumour cells) and ‘major’ residual mediastinal disease (>10% viable tumour cells). These mediastinal morphometric grading groups, together with the percent decrease of SUVmax of the primary tumour, were correlated with survival to establish an algorithm for prognostic restaging.

Results: The median and 5-year overall survival for the 30 patients was 36.4 months and 30%, respectively. The median decrease of SUVmax on the primary tumour between baseline and repeat PET scan was 60%, and this value was used as cut-off. A >60% decrease compared to a <60% decrease of SUVmax resulted in a median survival time of 57.5 versus 18.3 months and 5-year overall survival 47% versus 13%, respectively; log-rank p=0.01, HR 0.34 (95%CI 0.12-0.74). No patient with ‘major’ residual mediastinal disease survived 5 years, while 5-year overall survival was 43% both in patients with mediastinal clearance as well as in those with ‘minor’ residual mediastinal disease. Combined prognostic stratification resulted in two subgroups: patients with downstaging or persistent ‘minor’ mediastinal LN involvement and >60% decrease of SUVmax on the primary tumour were allocated as ‘Good Prognosis group’ (n=13). Patients with downstaging or persistent ‘minor’ mediastinal LN involvement and <60% decrease of SUVmax on the primary tumour were pooled with patients having persistent ‘major’ mediastinal LN involvement and allocated as ‘Poor Prognosis group’ (n=17). The median and 5-year overall survival for these Good and Poor Prognosis groups were “not reached” versus 18.3 months, and 62% versus 6%, respectively; log-rank p<0.0001, HR 0.18 (95%CI 0.06-0.38).
Conclusions: These data suggest: (1) persistent ‘minor’ pN2-disease following induction chemotherapy does not always exclude favourable outcome after surgery; (2) serial FDG-PET is able to select surgical candidates amongst patients with persistent ‘minor’ pN2-disease or with mediastinal clearance; (3) persistent ‘major’ pN2-disease has a poor prognosis and should not be considered for surgery.

Session A2: Imaging - Prognostic Determinants
Monday, September 3

A2-01 Imaging - Prognostic Determinants, Mon, 13:45 - 15:30

Prognostic significance of AJCC T2 descriptor-visceral pleura invasion, hilar atelectasis or obstructive pneumonitis for stage IB non-small-cell lung cancer (NSCLC) is dependent on tumor size

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Background: The T2 descriptor in the AJCC staging for non-small-cell lung cancer (NSCLC) contains several non-size based criteria in addition to the criterion of tumor size greater than 3 cm. It remains unknown if there are survival differences between patients whose tumors were staged according to these non-size based criteria when compared to patients whose tumors were staged according to tumor size.

Methods: We analyzed 10,545 stage IB NSCLC patients from the California Cancer Registry (CCR) from 1989 to 2003. These patients were staged as IB disease according to three non-overlapping main criteria: 1) tumor size [T2S]; 2) visceral pleura invasion, hilar atelectasis or obstructive pneumonitis [T2P]; 3) main bronchus involvement ≥ 2 cm from the carina [T2C]. Univariate survival analyses were conducted using the Kaplan-Meier method. Multivariate survival analyses were performed using Cox proportional hazards ratios.

Results: 5385 (51.1%) IB patients were staged according to tumor size [T2S], 4557 (43.2%) patients were staged by visceral pleura invasion, hilar atelectasis or obstructive pneumonitis [T2P], and 603 (5.7%) patients were staged by main bronchus involvement ≥ 2 cm from the carina [T2C]. The 5-year survival and median OS of these IB patients with tumor 3 cm or smaller had survival similar to stage IA NSCLC tumors that were 3 cm or smaller had survival similar to stage IA NSCLC patients.

The T2 descriptor in the AJCC staging for non-small-cell lung cancer (NSCLC) contains several non-size based criteria. The prognostic significance of the T2C criterion requires further studies.

Cox proportional hazards model showing prognostic significance of various AJCC T2 descriptors.

<table>
<thead>
<tr>
<th>T2 descriptor</th>
<th>Number of patients</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2S</td>
<td>5385</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2P &gt; 3 cm</td>
<td>2960</td>
<td>1.127</td>
<td>(1.056-1.202)</td>
<td>0.0003</td>
</tr>
<tr>
<td>T2P ≤ 3 cm</td>
<td>1597</td>
<td>0.869</td>
<td>(0.796-0.948)</td>
<td>0.0016</td>
</tr>
<tr>
<td>T2C &gt; 3 cm</td>
<td>424</td>
<td>0.975</td>
<td>(0.841-1.130)</td>
<td>0.7343</td>
</tr>
<tr>
<td>T2C ≤ 3 cm</td>
<td>179</td>
<td>0.863</td>
<td>(0.693-1.075)</td>
<td>0.3985</td>
</tr>
</tbody>
</table>

Adjustment included: age at diagnosis, gender, race, socioeconomic status, marital status, histology, histologic grade, tumor lobar location, surgical treatment, chemotherapy and radiation.

T2S-T2 descriptor: by size only
T2P-T2 descriptor: visceral pleura invasion, hilar atelectasis or obstructive pneumonitis
T2C-T2 descriptor: main bronchus involvement ≥ 2 cm from carina

A2-02 Imaging - Prognostic Determinants, Mon, 13:45 - 15:30

Preliminary experience with mediastinal staging of patients with non-small cell lung cancer using endobronchial ultrasound (EBUS/TBNA)

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Background: Treatment and prognosis of patients with non-small cell lung cancer depend on the stage of the disease at the time of the diagnosis. Mediastinoscopy has been the golden standard for staging of the mediastinum for many years, and it has been proven that the false negative rate of N2-disease by this procedure is near 20% or more. The consequence of this is often a futile thoracotomy without benefit for the patient.

We would like to report the results of our preliminary experience with EBUS/TBNA for staging of the mediastinum.

Methods: A total of 152 consecutive patients were examined by EBUS/TBNA during the first year (2006) the method was used in our department. The indication was mediastinal staging in 82 patients (53.9%). The remaining 70 patients were examined because of an undiagnosed mediastinal mass, follow-up after resection of NSCLC, or restaging after chemotherapy. The 3 examiners had no previous experience with endoscopic ultrasound, but were trained for a period of 2 days in another institution with experience in the method.

The examinations of the 82 patients were carried out in general anaesthesia with a linear scanner (BF-UC160F, Olympus). Cytological samples were taken by 22G needle aspiration (NA-201LSX-4022, Olympus) from all lymph node stations visualized. Patients positive for N2 or N3-disease (n=32) by EBUS/TBNA were not examined further, but referred to oncological treatment. Patients without N2 or N3-disease

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