Preoperative chemotherapy with and without additional radiochemotherapy: benefit and risk for surgery of stage III non-small cell lung cancer

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Abstract

Objective: Multi-modality approaches are increasingly employed to improve prognosis in surgically treated stage III non-small cell lung cancer (NSCLC). Risk and benefit of the preoperative therapeutic chemotherapy or combined radiochemotherapy on surgical morbidity and mortality are still a matter of debate. Methods: In 1995, a national phase III trial was started to compare (arm A) preoperative chemotherapy followed by twice-daily chemoradiation and consecutive surgery, with (arm B) preoperative chemotherapy alone followed by surgery and consecutive radiotherapy. An interim analysis with 277 patients was performed to assess surgical risk and complication rates. Results: Of the 385 patients, 273 (71%) underwent thoracotomy, 130 (73%) in arm A and 143 (69%) in arm B. Of the 273 patients undergoing thoracotomy, 168 had stage IIIB disease. Complete resection (R0) was achieved in 212 patients (78%), 104 in arm A (80%) and 108 in arm B (76%) (P = n.s.). There was no difference in the proportion of complex resections between treatment arms (41% in arm A; 48% in arm B). Whilst bronchial stump insufficiency (3.8 vs 2.1%) and bleeding requiring re-thoracotomy (1.5 vs 0.7%) prevailed slightly in arm A, the occurrence of pneumonia divided similar on both treatment arms (4.6 vs 4.9%). Surgical mortality reached 6.1% in arm A (8/130) and 5.6% in arm B (6/143) (P = n.s.). Conclusions: In both treatment arms, a similar percentage of patients could be forwarded to surgery, even in stage IIIB disease. Bimodality induction seems to be superior with regard to resection rates (R0) (n.s.), but was associated with a higher complication rate, especially bronchial stump insufficiency.

Keywords: Additional radiochemotherapy; Benefit and risk of surgery; Stage III NSCLC

1. Introduction

In stage III non-small cell lung cancer (NSCLC) proven by mediastinoscopy, locoregional treatment alone results in 5-year survival rates of less than 10% [1]. In recent years, evidence is growing from several phase II-trials that approaches of trimodality therapy, including preoperative radiotherapy sequential or simultaneous to neoadjuvant chemotherapy, may improve survival rates [2–5]. However, treatment related mortality rates rose up to 10% and have been mainly related to surgery [2]. The impact of preoperative bimodality induction on surgical morbidity and mortality is still unclear. Thus, we started a multi-institutional phase III-trial in 1995 that compares chemotherapy followed by twice-daily chemoradiation prior to surgery with preoperative che-mo-therapy alone followed by surgery and consecutive radiotherapy [6].

We report on an interim analysis in this closed trial to assess the impact of preoperative chemoradiation additional...
to chemotherapy on resectability, on necessity and feasibility of complex resections, and on surgical morbidity and mortality in the neoadjuvant treatment setting of stage III NSCLC.

2. Patients and methods

2.1. Eligibility criteria and preoperative assessment

After approval by the Ethics Committee of the University of Münster and the local Ethics Committees of the other participating sites, the trial started in October 1995. Written consent is obtained in all cases. The study has been designed as an open multi-institutional phase III-trial, prospectively entering 500 patients, and is recently closed. Patients with histologically documented non-small cell lung cancer of stages IIIA and IIIB were eligible when meeting the following selection criteria: mediastinal lymph node staging by mediastinoscopy, age under 70 years, a performance score of ECOG 0 or 1, a predicted postoperative forced expiratory volume at 1 s greater than 1 l (if mandatory calculated by lung perfusion scanning), no prior oncological treatment (chemotherapy, radiotherapy, surgery), no other previous or concurrent malignancies, no contradictions to surgery because of medical reasons like cardiac infarction or unstable angina pectoris 6 months before study entry, or cardiac disability of NYHA (New York Heart Association) class III/IV.

All patients were staged according to the International Staging System [7]. Since the trial started before the reclassification of the Mountain criteria in 1997, centrally located T3 N0/1-tumors were included as stage IIIA neoplasms [8]. These were defined by diffuse infiltration less than 2 cm from the main carina or radiographically proven infiltration of the parietal pericard. N2-disease at mediastinoscopy led to inclusion as stage IIIA too in patients without T4-tumors. Peripherally located T3 N0/1-tumors with chest wall involvement were excluded from the study. The inclusion criteria for stage IIIB were N3-disease proven by mediastinoscopy, diffuse mediastinal involvement found at mediastinoscopy or in computed tomography, or infiltration of the main carina, the spine, the pulmonary artery, the aorta, or the superior vena cava in computed tomography or MRI. Patients with supraclavicular N3-disease, infiltration of the myocardium, ipsilateral satellite pulmonary nodules in the same lobe, or malignant pleural effusion were not eligible. After staging, the patients were stratified according to center and stage (IIIA vs IIIB) and randomized to receive either treatment A or B (Fig. 1).

Preoperative patient assessment was performed 2 weeks after completion of combined chemoradiation (arm A) or chemotherapy (arm B), respectively, and included standard laboratory parameters, chest X-ray, bone scan and CT scans of thorax, abdomen and brain, as well as bronchoscopy. In selected patients, angiography of the pulmonary artery, aorta or vena cava was performed to define suspected or present vessel infiltration. Additionally, all patients underwent cardiovascular risk assessment and cardiopulmonary function tests. Clinical response was judged according to the guidelines of the South-West Oncology Group (SWOG) [9].

2.2. Statistical methods

To evaluate statistical significance of proportion we performed two-sided Fisher’s Exact Test. Two-sided P-values less than 0.05 were considered significant. In addition, where appropriate, we calculated two-sided exact 95% confidence intervals (CI) for binominal proportions.

2.3. Study design and treatment

All patients started with 3 cycles of chemotherapy consisting of cisplatin 55 mg/m² (day 1 + 4) and etoposide 100 mg/m² (days 1 − 4) as shown in Fig. 1. The interval between the cycles was 3 weeks.

In arm A, patients were then scheduled to combined chemo- and radiotherapy. Five days a week, patients received fractions of 1.5 Gy twice daily (interval at least 6 h) until the target volume dose (TVD) of 45 Gy was reached (days 64–82). Concurrently carboplatin (100 mg/m²) and vindesine (3 mg absolute) were administered on days 64, 71,
and 78. Four to eight weeks after completion of combined chemoradiotherapy, patients free of distant metastases were scheduled for surgery.

In arm B, patients without distant metastases were referred for surgery without further neoadjuvant therapy and received after complete resection radiotherapy with a TVD of 54 Gy (1.8 Gy daily).

Patients with unresectable tumors, refusal of surgery or incomplete resection went on in arm A to further twice-daily radiation up to a TVD of 24 Gy. In arm B these patients received a TVD of 68.4 Gy (1.8 Gy daily).

2.4. Eligibility for surgery

Patients were considered eligible for surgery if staging demonstrated an improved or stable disease, and medical as well as functional operability was given. These judgements were made in each participating site by a local interdisciplinary conference involving the thoracic surgeon, the pneumologist, the medical oncologist and the radiooncologist. Thoracotomy was performed with the aim of achieving complete resection of the tumor (R0, resection margin microscopically free of tumor cells) and complete mediastinal lymph node sampling or dissection [10].

3. Results

3.1. Patient characteristics and response to preoperative treatment

A total of 385 patients were evaluated for surgery (arm A 179; arm B 206), of whom 273 patients were judged eligible and scheduled for surgery (arm A 130/179; 73%; arm B 143/206; 69%) (P=n.s.). (Tables 1 and 2). Of patients undergoing surgery the proportion of those with stage IIIB-disease was 62% in arm A and 61% in arm B. Pretreatment characteristics of patients undergoing thoracotomy are outlined in Table 1. Sixty-five of the patients with stage IIIA (n=105) had N2-disease proven by mediastinoscopy, 40 patients had centrally located T3-tumors with negative mediastinoscopy. Of those with IIIB-disease (n=168), 112 had T4-tumors.

Preoperative response distribution of patients undergoing thoracotomy was as follows:

Arm A (n=130) complete response, 12 (9.2%); partial response, 92 (70.8%); no change, 24 (18.5%). Arm B (n=143) complete response, 5 (3.5%); partial response, 94 (65.7%); no change, 40 (28%). Moreover, despite staged as progressive disease, in arm A 2 patients (1.5%) and in arm B 4 patients (2.8%) underwent thoracotomy. The difference of response rates between both treatment arms was not statistically significant. Response rates were in arm A 80% and arm B 69.2%.

Table 1

<table>
<thead>
<tr>
<th>Pretreatment patients characteristics</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM-Stage</td>
<td>130</td>
<td>143</td>
</tr>
<tr>
<td>III A</td>
<td>49</td>
<td>56</td>
</tr>
<tr>
<td>T3 N0/1 M0</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>T1-3 N2 M0</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>III B</td>
<td>81</td>
<td>87</td>
</tr>
<tr>
<td>T4 N0/1 M0</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>T4 N2 M0</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>T1-3 N3 M0</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>T4 N3 M0</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Age, years (median)</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>106 (82)</td>
<td>112 (78)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>24 (18)</td>
<td>31 (22)</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 1 (%)</td>
<td>15 (12)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>ECOG 0 (%)</td>
<td>115 (88)</td>
<td>126 (88)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC (%)</td>
<td>81 (62)</td>
<td>88 (62)</td>
</tr>
<tr>
<td>AC (%)</td>
<td>33 (26)</td>
<td>42 (29)</td>
</tr>
<tr>
<td>LCC (%)</td>
<td>16 (12)</td>
<td>13 (9)</td>
</tr>
</tbody>
</table>

PS, performance score; SCC, squamous cell carcinoma; AC, adenocarcinoma; LCC, large cell carcinoma.

3.2. Feasibility of surgery

Surgery followed the end of chemoradiotherapy in arm A or the end of sole chemotherapy in arm B after an interval of 45 (median; interquartile interval, 17.5) and 36 (median; interquartile interval, 14) days, respectively. In the majority of cases (134/273, 49%) lobectomy was sufficient for tumor removal. There were no differences between arm A (63/130, 48%) and arm B (71/143, 50%). The necessity of pneumonectomy was also similar among the groups (arm A/arm B: 43/130, 33% vs 45/143, 31%) as was the amount of bilobectomies (arm A/arm B: 7/130, 5.4% vs 6/143, 4.2%) and non-resectional thoracotomies (arm A/arm B 12/130, 9.2% vs arm B 12/143, 8.4%).

Table 2

Resectability and surgical procedure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients undergoing thoracotomy</th>
<th>Complete resection (R0, %)</th>
<th>Complex resectiona (%)</th>
<th>Mean operation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>IIIA</td>
<td>49</td>
<td>38 (78)</td>
<td>16 (33)</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>81</td>
<td>66 (81)</td>
<td>37 (46)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>130</td>
<td>104 (80)</td>
<td>53 (41)</td>
</tr>
<tr>
<td>Arm B</td>
<td>IIIA</td>
<td>56</td>
<td>46 (82)</td>
<td>22 (39)</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>87</td>
<td>62 (71)</td>
<td>46 (53)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>143</td>
<td>108 (76)</td>
<td>68 (48)</td>
</tr>
</tbody>
</table>

Total 273 212 (78) 121 (44) 167 ± 71

a Extended lung resections requiring procedures such as bronchus sleeve resection, intrapericardial resection, tracheobifurcal resection, resections of the chest wall or the diaphragm, resections of the vena cava, aorta, pulmonary artery or atrium of the heart.
Complete resection of the primary tumor with systematic lymphadenectomy or lymph node sampling was possible in 78% of patients (212/273). Resectability according to the lymphadenectomy or lymph node sampling was possible in (121/273, 44%; IIIA 38/105, 36%; IIIB 83/168, 49%). Two recent trials, employing preoperative neoadjuvant chemotherapy or chemoradiotherapy followed by surgery [11]. In trimodality treatment approaches, favorable 3-year survival rates of 40–60% can be achieved for patients with complete resection and a histomorphologic complete response in removed mediastinal lymph nodes [2–5]. However, considerable treatment related mortality rates approaching 10% and mainly attributed to the surgical intervention, have been reported [2].

In the present interim analysis, bimodality induction seemed to be superior to sole neoadjuvant chemotherapy, particularly as there is a trend toward an improved resectability rate in patients pretreated with chemotherapy and chemoradiation in contrast to mere chemotherapy. A substantial proportion of patients were encountered with complex resections (121/273, 44%; IIIA 38/105, 36%; IIIB 83/168, 49%). Two recent trials, employing preoperative chemoradiation, reported similar rates of complex resections of 30–40% in stage IIIA and almost 60% in stage IIIB surgery). Considering late surgical mortality (>30 days postoperatively) further two patients succumbed to pneumonia, one at day 34 (arm A) and one at day 33 (arm B) after perioperative cerebellar infarction.

Sixty-two percent of patients (n = 170) (arm A 80, 62%; arm B 90, 63%) recovered without complications. Those with complications are outlined in Table 3. Moreover, in 13 patients prolonged chest tube therapy (n = 8; arm A, 5, arm B, 3), transient neurologic disorder (n = 3; arm A, 1; arm B, 2), and chylothorax (n = 2; arm A, 1; arm B, 1) were reported. Further complications, occurring once each, comprised in arm A pneumothorax, and putrid bronchitis, and in arm B perioperative occurrence of stroke, bronchus stenosis, lung embolism, seroma of chest wall, cardiac failure with lung edema, and cardiac arrest with resuscitation.

### Table 3

<table>
<thead>
<tr>
<th>Stage</th>
<th>n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pneumonia (%)</th>
<th>Stump insufficiency (%)</th>
<th>Re-thoracotomy (bleeding; luxatio cordis) (%)</th>
<th>Respiratory insufficiency (demanding prolonged respirator therapy) (%)</th>
<th>Nerve lesion (%)</th>
<th>Secrete retention (demanding bronchoscopy) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A IIIA</td>
<td>49</td>
<td>4 (8.2)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>2 (4.1)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>IIIB</td>
<td>81</td>
<td>2 (2.5)</td>
<td>4 (4.9)</td>
<td>2 (2.5)</td>
<td>3 (3.7)</td>
<td>4 (4.9)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>6 (4.6)</td>
<td>5 (3.8)</td>
<td>2 (1.5)</td>
<td>4 (3.1)</td>
<td>6 (4.6)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Arm B IIIA</td>
<td>56</td>
<td>2 (3.6)</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>2 (3.6)</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>IIIB</td>
<td>87</td>
<td>5 (5.7)</td>
<td>2 (2.3)</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
<td>3 (3.4)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td>7 (4.9)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>5 (3.5)</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>Total</td>
<td>273</td>
<td>13 (4.8)</td>
<td>8 (3.7)</td>
<td>4 (1.5)</td>
<td>7 (2.6)</td>
<td>11 (4)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients undergoing thoracotomy.

#### 3.3. Morbidity and mortality of surgery

A total of 16 patients (arm A 8/130, 6.2%, arm B 8/143, 5.6%) had lethal complications associated with surgery (P = n.s.). 30-day-mortality rate was 2.9% and did not differ significantly between the treatment arms (arm A 4/130; arm B 4/143) (P = n.s.). Late mortality was 2.9% (arm A 4/130; arm B 4/143) (P = n.s.). Of note, one of these patients (arm A) underwent surgery, even strictly abrogated in the protocol. Post-mortem examination revealed a dehiscent suture of the pulmonary vessels. Despite the initial judgement of inoperability and thus a TVD of 68 Gy in twice-daily fractions, he went on to palliative left sided lobectomy due to refractory pneumonia 4 months after the end of radiotherapy.

Main cause of surgical mortality was pneumonia with consecutive respiratory insufficiency (n = 7) and bronchial stump insufficiency (n = 5). Despite employing different surgical strategies including bone spongiosis (n = 2), transpericardial occlusion (n = 1), myoplasty (n = 1), fibrin glue occlusion (n = 2), chest tube and antibiotics (n = 1), 5 out of 7 patients (pneumonectomy, n = 3; bilobectomy, n = 1; lobectomy, n = 1) with bronchial stump insufficiency (arm A, 4/arm B, 1) died due to this problem (14, 154, 170, 279 and 403 days after surgery). Considering late surgical mortality (>30 days postoperatively) further two patients succumbed to pneumonia, one at day 34 (arm A) and one at day 33 (arm B) after perioperative cerebellar infarction.

#### 4. Discussion

In the last decade, evidence has been growing that the poor survival rates in stage III non-small cell lung cancer can be improved by multi-modality treatment using neoadjuvant chemotherapy or chemoradiotherapy followed by surgery [11]. In trimodality treatment approaches, favorable 3-year survival rates of 40–60% can be achieved for patients with complete resection and a histomorphologic complete response in removed mediastinal lymph nodes [2–5]. However, considerable treatment related mortality rates approaching 10% and mainly attributed to the surgical intervention, have been reported [2].
Apart from an advanced tumor stage, fibrosis and scarring related to the neoadjuvant treatment can render lung resection more complex. However, the need of complex resections as well as the necessity of pneumonectomies and lobectomies was more or less similar between the two treatment arms.

In addition to complete resection three phase II-trials, employing chemoradiation prior to surgery, emphasized a favorable histomorphologic response in the resection specimens, either of the mediastinal lymph nodes [2,3] or the mediastinal lymph nodes and additionally the primary tumor [5], as the most important predictor for long-term outcome. This gives rise to speculation on the contribution of surgery to the long-term outcome in the trimodality treatment setting. Thus, a large phase III-trial in stage IIIA (N2) disease (Intergroup trial 0139) is addressing the additional impact of surgery in this treatment approach. The significance of this issue is emphasized by mortality rates in conjunction with trimodality therapy that range about 10% and are clustering with surgery [2].

Particularly radiotherapy employed sequentially or simultaneously to neoadjuvant chemotherapy has been assumed to significantly increase surgical risk as it may promote fibrosis, bleeding and bronchial stump insufficiency [14]. In fact, bronchial stump insufficiency (3.8 vs 2.1%) as well as significant bleeding requiring re-thoracotomy (1.5 vs 0.7%) dominated in arm A of the present trial. As patients with these complications did not cluster substantially beyond or beneath the median time interval of 45 days between the end of chemoradiation and surgery, there is no evidence that performing surgery too late or too early in the time course of treatment has precipitated these adverse events. A monoinstitutional trial enrolling IIIB patients, who were preoperatively treated with radiation twice-daily in addition to chemotherapy, reported on a bronchial stump insufficiency rate of only 4.8% [4]. Another trial exclusively enrolling patients with stage IIIA-disease in a multi-institutional approach with conventional radiotherapy in addition to preoperative paclitaxel-containing chemotherapy reported a rate of 12.5% [15]. When applying a preoperative target volume dose of 60 Gy concomittant to chemotherapy, bronchial insufficiency developed even in 23% of cases [14]. These differences between the trials may depend on dosing and application of radiotherapy, but also on different surgical techniques. We experienced no continued occurrence of this complication, when in the multi-center setting of our trial participating institutions consistently sealed the bronchial stump with horizontal mattress sutures and protected the stump with a flap of intercostal muscle or other viable tissue. The importance of an appropriate surgical technique in this regard has also been emphasized by others [13,16,17].

Beyond bronchial stump insufficiency pneumonia was the major cause for surgical mortality with three patients in arm A and four patients in arm B. All but two succumbed early after surgery (<30 days). Moreover, one patient died due to right heart failure 3 days after right-sided pneumonectomy, and another expired due to a dehiscent suture of the pulmonary vessels. Albeit surgery in this case violated the protocol he was evaluated as surgical mortality.

In conclusion, overall surgical risk was similar with or without preoperative radiation in this phase III-trial. Preoperative bimodality induction seems to be superior compared to sole preoperative chemotherapy in order to achieve complete resection (n.s.). Bronchial stump insufficiency dominated in the patient cohort with neoadjuvant chemotherapy followed by chemoradiation, and had an impact on surgical mortality. Adopting appropriate surgical techniques, bronchial stump insufficiency could be almost completely eliminated.

Acknowledgements

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(1) Lung Clinic, Hemer;
(2) St Raphael Hospital, Osterkappeln/Osnabrück;
(3) Kreiskrankenhaus, Diekholzen/St Bernward Hospital, Hildesheim
(4) Clinic for Pneumology and Thoracic Surgery, Berlin-Buch;
(5) University Hospital, Homburg/Saar;
(6) Clemens Hospital, Münster;
(7) Krankenhaus der Barmherzigen Brüder, Trier;
(8) Klinikum Kreis Herford, Herford;
(9) Kreiskrankenhaus, Aurich/Hans-Susemihl-Hospital, Emden;
(10) University Hospital, Münster.

Further 5 hospitals (with lower case load) are not mentioned. We thank all participating hospitals for their active support during the study period.

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References


Appendix A. Conference discussion

Dr A. Turna (Istanbul, Turkey): You stated that approximately 60% of the patients underwent thoracotomy after randomization. Could you please tell us the number of patients who could not be operated because of the excessive side effects or toxicity of chemotherapy and/or radiotherapy and the number of patients who could not be operated because of the progression of the disease after the radiochemotherapy protocol?

Semik: I mentioned that we had 385 patients evaluated for surgery, and 112 patients who were not operated were locally or distantly progressed on the one side, and otherwise functionally inoperable, so these patients were excluded from surgery.

The toxicity is mainly due to esophagitis (grades 3 and 4) in arm A. This reached nearly 20%. So this is an relevant side effect of that bimodality induction. Concerning the nearly equal follow-up in both treatment arms (in the intermediate evaluation), nowadays we proceeded more following arm B without chemoradiation because of that side effect.

Dr T. Dosis (Athens, Greece): I realize that you have more bronchopleural fistula, or, what you said, bronchial stump insufficiencies, in the arm with radiotherapy, but you didn’t find any difference in early mortality and long-term survival. So my question is, do we have to put our patients in radiotherapy preoperatively, and do you think that this higher rate of bronchopleural fistula that is about 5% or something like that is due to radiotherapy?

Semik: Concerning the last question, I think the radiochemotherapy may be responsible, but after our learning curve in the study group, the complication of that kind was normalized. So if you are experienced in thoracic surgery and operating on those pretreated patients, I think you can drop the complication rate to a normal level. This would be no reason to stop that kind of therapy.

Dr Dosis: If there is no advantage, why continue giving radiotherapy?

Semik: Up to now it seems that there is no relevant benefit for the bimodality induction, but the final analysis is still ongoing. Later I will report you about the final results and if any subgroups with preoperative radiochemotherapy improved in longterm survival.

Dr K. Athanassiadis (Athens, Greece): I would also like to ask you a similar question about the bronchial fistula you had. What was the total percentage of fistulae you had after pneumonectomy? How do you protect the bronchus after either chemotherapy or radiotherapy or both and I would like to know if this is your strategy in all cases?

Semik: In the early phase of our study we didn’t protect the bronchus anastomosis routinely, but after that higher incidence in the beginning of our study, we did it routinely. We had 3 bronchial stump insufficiencies after pneumonectomy, one after bilobectomy, and one after lobectomy.

Athanassiadis: And how did you protect your stump? What did you use?

Semik: Different techniques were used for bronchial stump or anastomoses protection, responsible was the local thoracic surgeon of the participating hospitals. Normally, pedicled flaps of pleural tissue, intercostal muscle or mediastinal thymic tissue were used.

Dr O. Kshivets (Siauliai, Lithuania): My question is do you plan to change to the cisplatin regimen for example on gemzar? It’s less toxic and more effective. And I have some comments. I advise you to give these patients radiotherapy less than 50 Gy. You treated with 54 Gy according to the last randomized treatment. Gy. According to the last You say the toxicity is mainly due to esophagitis (grades 3 and 4) in arm A. This reached nearly 20%. So this is an relevant side effect of that bimodality induction. Concerning the nearly equal follow-up in both treatment arms (in the intermediate evaluation), nowadays we proceeded more following arm B without chemoradiation because of that side effect.

Dr A. Turna: Thank you very much...