Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response

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Introduction: Optimal preoperative treatment of stage IIB (Pancoast)/III non-small cell lung cancer (NSCLC) remains undetermined and a subject of controversy. The goal of our study is to confirm feasibility and pathological response rates after induction chemoradiation (CRT) in our community-based treatment center. Patients and methods: Patients were selected according to functional and resectability criteria. Induction treatment comprised 3D conformal 4500 cGy radiotherapy delivered to the primary tumor and pathologic hilar and/or mediastinal lymph nodes on CT scan with an extra-margin of 1—1.5 cm. Concurrent chemotherapy regimen was cisplatinum 20 mg/m² d1—d5 and etoposide 50 mg/m² d1—d5, d1—5 d29—33. Within 3—4 weeks after CRT completion, operability was re-assessed accordingly. Surgery was performed 4—6 weeks after CRT completion in patients (pts) deemed resectable. Inoperable pts were referred for a 20—25 Gy boost extra-cycle of cisplatinum + etoposide.

Results: From 1996 to 2005, 107 pts were initially selected for treatment and received induction chemoradiation (stage IIB-Pancoast 18, IIIA 58 and IIB 31, squamous cell carcinoma 48%, adenocarcinoma 44%, large-cell undifferentiated carcinoma 14%). After preoperative evaluation, 72 pts (67%) had a thoracotomy (pneumonectomy 21, lobectomy 45, bilobectomy 5) and all but one (unresectable tumor) had a macroscopic complete resection. During the 3-month postoperative time, five patients (6.9%) died, four after pneumonectomy (right 3, left 1). The analysis of tumoral samples showed a pathological complete response rate or microscopic residual foci of 39.5%. Median follow-up time was 22.3 months (survivors: 36.8 months), 2-year and 3-year overall survival rates were 55% and 40%, respectively (median = 26.7 months) for all the intention-to-treat population (n = 107), 62% and 51% (median = 36.5 months) for 71 resected pts, 41% and 16% for 36 non-resected pts (median = 19.1 months). On multivariate analysis, surgical resection and tumoral necrosis (>50% (or pathological complete response) were the most pertinent predictive factors of the risk of death (hazard ratio = 0.50 and 0.48, p = 0.006 and 0.038, respectively). Conclusion: Surgery was feasible after induction chemoradiation, particularly lobectomy in PS 0—1, stage IIB (Pancoast)/III NSCLC pts but pneumonectomy carries a high risk of postoperative death (particularly, right pneumonectomy). Pathological response to induction chemoradiation was complete in 39.5% of patients and was a significant predictive factor of overall survival.

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Keywords: Induction; Chemoradiation; Surgery; Non-small cell lung cancer; Combined modality treatment

1. Introduction

Optimal treatment strategy of patients (pts) presenting with stage IIIA/B and superior sulcus T3N0-Pancoast (stage IIB) non-small cell lung cancer (NSCLC) has yet to be determined. Surgery alone generally results in a poor outcome with median overall survival time (MST) of 10—15 months and few long-term survivors (less than 10%) [1—3]. Several phase III studies have shown conflicting results concerning the role of induction chemotherapy (CT) + surgery versus surgery alone (±postop. RT) with a significant increase in MST in Roth et al. [3] (64 months vs 11 months, p = 0.008), Rosell et al. [2] (26 months vs 8 months, p < 0.001) and Pass et al. [1] studies (28.7 months vs 15.6 months, p = 0.095) while Depierre et al. [4] observed a less important difference (25.0 months vs 18.9 months, p = 0.15). A more recent phase II study by Betticher et al. [5] using a 3rd generation CT regimen (cisplatinum and docetaxel) has shown promising results after induction CT with a median overall survival time of 33 months among 90 stage IIIA(N2)
patients (median follow-up time: 32 months). In this study, mediastinal clearance and complete resection were strong predictors of survival on multivariate analysis.

Induction chemoradiation (CRT) is a promising therapeutic concept in locally advanced NSCLC, from stage IIB-Pancoast to stage IIIA(N2) and operable IIIB (mainly T4N0–1), whereas non-Pancoast stage IIB are accessible to upfront surgery. While CT alone yields pathological complete response (pCR) rates ranging from 3.7—19% [1—5], CRT surgery. While CT alone yields pathological complete response (pCR) rates ranging from 3.7—19% [1—5], CRT achieves 21—65% pCR rates in three successive phase II SouthWest Oncology Group (SWOG) and Intergroup (INT) trials [6—8] among stage IIB (Pancoast) and IIIA patients. Pathological response to induction CRT was associated with mediastinal clearance and complete resection were strong predictors of survival on multivariate analysis.

The goal of our confirmatory study was to reproduce the results of the previous SWOG and INT studies, using a similar regimen of 2 cycles of cisplatinum + etoposide chemotherapy and 4500 cGy radiotherapy delivered with a homogenous 5-field 3D conformal technique in a community-based comprehensive cancer center and thoracic surgery unit (Institut Sainte-Catherine and Centre Hospitalier Henri Duffaut, Avignon, France) among stage IIB/III NSCLC patients. Our primary endpoint was pathological complete response rate. Secondary endpoints were postoperative morbidity/mortality and survival.

2. Patients and methods
2.1. Eligibility criteria

Patients with potentially operable, locally advanced NSCLC, stage IIB (T3N0 superior sulcus, Pancoast) or stage III (bulky N2 and N3 excluded) with performance status (PS) ranging from 0 to 2 and age from 18 to 80 were proposed CRT after multidisciplinary validation of treatment indication (thoracic surgeon, pneumologist, radiation oncologist and medical oncologist).

Pretreatment evaluation included a thoracic and upper abdomen computed tomography scan (CT scan), a brain magnetic resonance imaging (MRI) and a bone scan. Positron emission tomography scan (PET scan) was used later on when it became routinely available in 2004. Mediastinoscopy was performed in case of doubtful lymph node involvement in the mediastinum on CT scan (or PET scan when available).

Definitive staging was assessed during a multidisciplinary discussion about treatment indication and the initial CT scan was systematically peer reviewed. For Pancoast tumors, indication for CRT was based on marginal resectability as assessed by the surgeon.

Additional eligibility criteria to treatment were an adequate pulmonary function (predicted forced expiratory volume in 1 s (FEV1) >40% or in between 30 and 40% with an adequate \( V_{O2_{max}} > 15 \text{ml/(kg)} \)) and biological parameters (leukocytes >4000/mm\(^3\), platelets >100,000/mm\(^3\), creatinine clearance >60 ml/min). Cardiac function was assessed by ultrasound in case of a cardiac history.

2.2. Study design and follow-up

Patients were given a radiotherapy (RT) regimen comprising 4500 cGy in 180 cGy fractions (fr.), 5 fr./week over 5 weeks using a uniform conformal 5-field technique. Gross tumoral volume (GTV) was delineated from an iodine-injected helical CT scan. Planned target volume (PTV) was extrapolated from GTV using an automated isotropic 10—15 mm expansion. Field arrangement was optimized per patient to ensure a coverage of 100% of PTV by 95% of the prescribed dose (according to the International Commission on Radiation Units (ICRU) standards). Dose to spinal cord had to be maintained under 4500 cGy.

Concurrent CT consisted of two cycles of cisplatinum and etoposide: \( P 20 \text{mg/m}^2/d_1—d_5 \) and \( d_{29}—d_{33} \), \( E 50 \text{mg/m}^2/d_1—d_5 \) and \( d_{29}—d_{33} \) (PE).

Three to four weeks after CRT completion, patients were reassessed by physical examination, thoracic, upper abdominal CT scan and blood tests. PET scan and/or mediastinoscopy were not routinely performed at that particular time of treatment schedule. In the absence of disease progression (i.e. stable disease or partial/complete response), patients were referred for surgery. In the case of tumor progression, patients were referred for salvage treatment with hypofractionated radiotherapy (25—30 Gy/10 fractions/2 weeks with or without 1 extra PE cycle).

Surgery was performed 5—6 weeks after CRT completion: lobectomy, bilobectomy or pneumonectomy were allowed, accessible hilar and mediastinal lymph nodes were systematically removed, appropriately labeled and separately analyzed by the pathologist. Wedge-resection was not allowed. When a pneumonectomy was performed, a pleural flap was made on the bronchial stump.

In case of contra-indication to surgery, a radiotherapy boost consisting of 2000—2500 cGy/10—15 fr. with concurrent PE (1—2 cycles) was performed.

Postoperative chemotherapy and/or radiotherapy were also allowed according to the same modalities in case of R1/2 surgical resection or in case of pN2 disease.

Acute complications from CRT were compiled from individual patient records and rated according to the National Cancer Institute; Common Toxicity Criteria scale version 2.0 (NCI CTC v2.0). Surgery perioperative morbidity and mortality was prospectively collected and recorded in the EPITHOR database of the Société Française de Chirurgie Cardio-Vasculaire et Thoracique (SFCVT).

Follow-up comprised physical examination, blood tests and chest plain radiographs (abdominal ultrasound or thoracic) and upper abdominal CT scan every 3 months for the first 2 years, every 6 months from the 3rd to the 5th year and annually thereafter. Brain MRI was performed annually for the first 2 years.

2.3. Statistical analysis

Categorical variables were illustrated by frequency tables. Their influence on the probability of CRT complication, postoperative complication and death was assessed by the chi-square test. Actuarial overall and relapse-free survival of the intention-to-treat population was estimated by the Kaplan–Meier method and comparisons between
groups were performed using the log rank test. The association between overall and relapse-free survival and a potential predictive or prognostic factor (clinical, pathological, staging, treatment) was investigated separately for each individual factor (univariate analysis). The predictive and prognostic impact of the variables was then investigated using the Cox multiple regression analysis: significant predictive factors in univariate analysis were introduced into a proportional hazard model and adjusted to potential confounding variables (gender, age, PS, stage). Hazard ratios illustrating the risk of death (HR) and corresponding 95% confidence intervals (CI95) are mentioned. All reported p values are two-sided.

3. Results

3.1. Patients

From 1996 to 2005, 107 patients received induction CRT. Patients’ characteristics are summarized in Table 1. There were 91 males and 16 females with a median age of 59 (range: 31—81). Most of them (94%) were PS 0—1 at the onset of treatment, a small proportion presenting with a PS 2 (6%).

Almost half of treated cancers were squamous cell carcinomas (48%), while others were either adenocarcinomas (38%) or undifferentiated large-cell carcinomas (13%); only one neuro-endocrine large-cell carcinoma was treated in our cohort (1%). The upper lobe was the most frequent tumor location (86 patients, 80%) followed by the lower lobe (17 patients, 16%); middle lobe and central tumors were infrequent (4 patients, 4%).

There were 18 patients with stage IIB (17%, all T3N0 Pancoast), 58 with stage IIIA (54%) and 31 stage IIIB tumors (29%). At initial evaluation, 66 patients (62%) were clinical N2 (cN2) with at least one significant adenopathy (i.e. short axis >1 cm) in the mediastinum on CT scan while 21 T4 patients were N0 and 20 T3 (Pancoast) patients were N0/N1.

3.2. Induction chemoradiation

Chemoradiation was discontinued in two patients: one sudden death due to an unrelated cause (rated as non-treatment related) occurred among the 107 patients who were proposed induction CRT and one patient refused treatment before CRT completion (RT dose delivered: 19.8 Gy + 1 cycle of PE).

Among the 105 remaining patients, 103 received two cycles of PE and 2 received only one: 1 patient with grade 3 fatigue and 1 patient with cisplatinum-induced renal failure. Regarding radiotherapy schedule, 102 patients received the planned 25 fractions of 180 Gy except three: two patients received only 24 fractions due to grade 3 fatigue, one patient received only 23 fractions due to an unrelated reason. Response to treatment was adequately assessed in 100 patients: there were 11 progression, 89 stable disease or partial/complete response.

Significant acute toxicity (grades 3—4, NCI-CTC v2.0 scale) due to induction CRT was infrequent in patients who completed treatment (n = 105): fatigue in three patients and renal failure in one patient were the cause of CT and/or RT discontinuation (Table 2). Febrile neutropenia, esophagitis and pneumonia were only transient events and did not interfere with treatment completion.

3.3. Surgery

Among the 105 patients who completed induction CRT, 72 patients had a thoracotomy (Fig. 1): there were 65 R0 resections, 4 R1 resections, 2 R2 resections, 1 exploratory thoracotomy only. The other 33 patients did not have any surgery (Fig. 1): 11 patients presented with tumor progression, 22 presented with a contraindication for surgery at the time of preoperative restaging and/or refused surgery (Table 3).
For stage IIB, IIIA and IIIB patients, 72%, 72% and 57% \((p = 0.488)\) were resected, respectively and there was only one unresectable stage IIIB (T4N2) tumor. Other categorical variables significantly influenced the probability of surgical resection such as age (median age: resected patients 58 years vs non-resected 66 years, \(p = 0.0084\)) and histology (proportion of resected patients: SCC 53%, adenocarcinoma 85%, large-cell carcinoma 71%, \(p = 0.00459\)). Gender, PS, tumor localization, clinical stage, year of treatment did not have a significant influence on the probability of being resected.

Type of surgery consisted in lobectomy in 45 patients (63%), bilobectomy in 5 patients (7%) and pneumonectomy in 21 patients (29%). Exploratory thoracotomy only was performed in one patient (1%).

### 3.4. Morbidity and mortality

Perioperative morbidity and mortality are detailed in Table 4. There were five perioperative deaths among 72 patients who underwent surgery (3-month mortality, crude rate: 6%): two within the first 30 days (1st month mortality, crude rate: 3%), three within the 30–90 days postop. Two patients died of pulmonary embolism at day 5 and 52, two of sepsis (empyema and multi-organ failure) at day 27 and 53, one of pneumonia (amiodarone-induced) at day 43. In these five patients, four had undergone pneumonectomy (right 3, left 1) and one lobectomy (upper right).

Significant perioperative morbidity occurred in 34 patients (Table 4): there were three complications in 5 patients, two in 6 patients and one in 23 patients. The most frequent events were arrhythmia \((n = 10)\), pneumonia \((n = 8)\), prolonged air leak \((n = 7)\), fistula \((n = 4)\), empyema \((n = 4)\), atelectasis \((n = 4)\) and hemorrhage \((n = 4)\). Others were infrequent but some of them lethal (3 or less events: recurrent laryngeal nerve palsy, pulmonary embolism, septicemia, lymphorrhea, bronchorrhea).

Almost 43% of all patients encountered at least one postoperative complication whatever the surgical procedure \((p = 0.76)\). Patients who underwent pneumonectomy had a higher number of complications than others with an average per patient of 1.82 against 1.3 but the difference was not statistically significant \((p = 0.15)\) and a significantly higher risk of death (crude rates: 19% vs 2%, \(p = 0.039\)).

### 3.5. Boost chemo-radiotherapy

Among the 33 patients who were not surgically resected, 28 had a boost RT only, 3 had a boost CRT and 2 had no other treatment. Among the 72 surgically resected patients, 57 had no other treatment, 11 had a boost CRT (2 R2 resections, 4 R1 resection and 5 pN2R0), 4 had chemo only (2 pN1R0, 2 pN2R0). There were no severe complications related to boost RT and/or chemo.

### 3.6. Pathological response and mediastinal clearance

Pathological response rate to induction treatment was evaluable in 71 surgically resected patients \((T_{\text{any}} N_{\text{any}}): a\)

### Table 2

<table>
<thead>
<tr>
<th>Toxicity (grades 3–4)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>1</td>
</tr>
<tr>
<td>Infection (febrile neutropenia)</td>
<td>2</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3(^b)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Who completed CRT.

\(^b\) Treatment discontinued before completion.

### Table 4

<table>
<thead>
<tr>
<th>No</th>
<th>Causes—comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>≤1 month postop.</td>
<td>2 Following pneumonectomy 2</td>
</tr>
<tr>
<td>1st–3rd month postop.</td>
<td>3 Following pneumonectomy 2, lobectomy 1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>

| Morbidity* |          |
| Non-procedure-specific |          |
| Arrhythmia | 10 Atrial and/or ventricular |
| Hemorrhage | 4 |
| Others non-lethal | 3 Septicemia 1, lymphorrhea 1, bronchorrhea 1 |
| Lobectomy-specific |          |
| Atelectasis | 4 |
| Prolonged air-leak | 7 |
| Pneumonia | 8 Infectious 6, toxic 2 |
| Pneumonectomy-specific |          |
| Fistula | 4 |
| Empyema | 4 Lethal 2 |
| Pulmonary embolism | 3 Lethal 2 |
| Recurrent laryngeal nerve palsy | 3 |
| Total | 50 In 34 patients |

\(^*\) 1–3 complication(s), 3 complications: 5 pts, 2 complications: 6 pts, 1 complication: 23 pts.

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\[\text{Cl: Contra-indicated at the time of preoperative restaging.}\]

\(^*\) Stage IIIB vs IIB/IIIA, \(p = 0.427\).
pathological complete response (or microscopic residual foci, i.e. necrosis >95%) was observed in 28 patients (39.5%), necrosis of tumoral tissues was over 50% but less than 95% in 16 patients (22.5%) and less than 50% in 27 patients (38%).

Mediastinal clearance was evaluable in 46 surgically resected patients with pathological lymph nodes at initial evaluation ($T_{\text{any}} cN2$): 28 patients (61%) were pN0/N1 while 18 patients (39%) still had metastasis in the mediastinum (pN2).

### 3.7. Relapse and survival

The median follow-up time for the intention-to-treat population ($n = 107$) was 22.3 months and for the surviving patients 36.8 months. At the time of statistical evaluation of survival, 2 patients were lost to follow-up, 38 patients were alive (disease-free 32, with disease 6) and 67 patients had died (due to cancer 53, due to treatment complications 5, due to a second cancer 1, due to a non-cancer event 6, due to an unrelated event 2).

Actuarial overall survival rate (OS) was 55% at 2 years, 40% at 3 years and the med. OS time was 26.7 months. For the patients who underwent surgery and were adequately resected ($n = 71$), OS was 62% at 2 years, 51% at 3 years and median OS time was 36.5 months. For the non-resected ($n = 36$), OS was 41% at 2 years, 16% at 3 years and med. OS time was 19.1 months (Fig. 2).

Actuarial relapse-free survival rate (RFS) was 40% at 2 years, 35% at 3 years and the median RFS time was 15.2 months. For the patients who underwent surgery and were adequately resected ($n = 71$), RFS was 43% at 2 years, 41% at 3 years and med. RFS time was 20.9 months. For the non-resected patients ($n = 36$), RFS was 28% at 2 years, 23% at 3 years and median RFS time was 12.6 months.

At the time of evaluation, 56 patients had relapsed and 3 others were lost to follow-up. The most frequent site of relapse was distant only (37 patients, 66%) followed by local only and concurrently local + distant (10 and 9 patients, 18% and 16%, respectively).

Occurring as a first site of relapse, local failures were all located ‘in-field’, i.e. within the volume receiving full dose RT. Regarding distant failure, the most frequent sites of relapse were brain ($n = 22$) followed by lungs ($n = 15$) and adrenal glands ($n = 6$); relapse in the bones ($n = 4$), liver ($n = 2$), extra-thoracic nodes ($n = 3$), pleura ($n = 1$) and others ($n = 3$) was infrequent. In seven patients, two or more sites were involved simultaneously (two in four patients, three in three patients).

### 3.8. Prognostic factors

On univariate analysis, resected patients had a significantly better outcome in terms of OS: MST of patients who underwent surgery was 36.4 months while in others MST was 19.1 months ($p = 0.002$). Among resected patients ($n = 71$), there was a trend for better outcome in lobectomy patients versus pneumonectomy patients (MST: 50.5 months vs 23.1 months, $p = 0.12$). The pathological response to induction CRT had also a significant influence on OS: in patients who underwent surgery, those who had a tumoral necrosis of more than 50% (or residual microscopic foci or a pathological complete response) had a better outcome than patients with less than 50% necrosis (MST 48.7 months vs 22.3 months, $p = 0.048$). Mediastinal clearance had no significant influence on OS: pN2 patients had a MST of 21.9 months while pN0—1 had a MST of 29.9 months ($p = 0.61$). Stage (IIb vs IIIA/B) also had a borderline influence on the risk of death ($p = 0.04$) that was not confirmed on multivariate analysis. Other categorical variables such as age, gender, PS, histological sub-type had no significant influence on OS.

On multivariate analysis (Table 5), surgical resection remained a significant predictive factor of OS with a risk reduction of death of 56% compared to boost CRT without surgery ($HR = 0.440$, 95% CI = [0.252—0.747], $p = 0.0026$). The risk reduction of death associated with tumoral necrosis (Fig. 3) also remained significant ($HR = 0.504$, 95% CI = [0.263—0.960], $p = 0.038$). Conversely, stage lost significance with a HR of 1.39 ($p = 0.36$).
4. Discussion

The optimal treatment of stage IIB/III NSCLC remains a subject of controversy. Several treatment strategies have been tested without drawing definitive conclusions. In our institution, we have been using induction CRT since the 90s following the report of SWOG-8805 trial [6]. In 1996, the implementation of 3D-conformal RT brought a substantial improvement in terms of tolerance and coverage of the GTV. In our series, all patients had 3D-conformal RT combined to a systemic dose cisplatinum-etoposide chemotherapy regimen; prophylactic mediastinal irradiation was not allowed. In this setting, CRT was feasible with only one refusal, one sudden death (unrelated cause) and 22 severe acute complications (grades 3—4 febrile neutropenia \( n = 2 \), pneumonia \( n = 2 \), esophagitis \( n = 6 \), others \( n = 12 \), no grade 5).

Among 105 patients who received CRT, 2/3 were actually operated on (\( n = 71 \), 68%). This resection rate was actually lower than in other series [6,8,10—14]. Among the 34 patients who were not resected, primary resistance to CRT (\( n = 11 \), 10%) was the first cause that is comparable to previously published data [14]. Contra-indication for surgery (\( n = 23 \), 22%) was the other cause due to various reasons (refusal, poor general status, anatomical presentation of tumor after induction treatment) indicating that selection of patients referred for surgery was very careful in our multidisciplinary practice.

Median survival of patients (\( n = 36 \)) who were not deemed resectable after CRT reached 19 months which is comparable to results in many series of inoperable stage III NSCLC [8,15—18]. Postoperative mortality rate (0—3 months) was acceptable in patients who received lobectomy (or bilobectomy) and was as low as 2%. Therefore, in our opinion, candidates for such surgical procedures at the time of initial work-up should be referred for trimodality treatment. On the contrary, a pneumonectomy was associated with a high risk of postoperative mortality (19%) and should not, in our opinion, be performed after CRT in stage III disease without using specific procedures like the reinforcement of bronchial stump with a pedicled muscle [19,20]. These results are interestingly similar to those of the INT-0139 trial [8].

Our primary objective was pathological response to CRT: an impressive complete response (or microscopic residual foci) rate of 39.5% compares favorably to previously published data [5,6,8,10—14]. Similarly, multivariate analysis of overall survival consistently showed that necrosis of primary tumor and lymph nodes (50% or more, 62.5% of patients) was significantly associated with a better outcome (\( p = 0.048 \)). These results might be due to the selection of patients and also the systematic use of conformal 3D radiotherapy. The role of mediastinal clearance could not be adequately assessed in our series because of the lack of systematic PET or mediastinoscopy before CRT was started. Therefore we assume that the absence of significant difference in the prognosis of pN0—1 versus pN2 patients might be due to the confounding effect of misclassification.

We are aware of the limitations of the preoperative staging during the period of time of our study (1996—2005) in terms of PET scan and mediastinoscopy. Therefore, survival results should be regarded with caution. Nevertheless, overall survival of resected patients was encouraging with a median of 37.5 months and a 3-year rate of 51%. These results are consistent with recently published data [Park, Kwong] based on 3-D conformal RT and seem to be superior to those observed after bimodality treatment like concurrent CRT alone [16—18] or induction chemotherapy followed by surgery [1—4]. Only a well designed randomized trial will answer to this question: in INT-0139, the surgery arm patients did not have a better outcome in terms of overall survival because of the excess mortality attributable to pneumo-
nectomy. Stage III disease is indeed a very heterogeneous group of patients and 'optimal' selection of patients to be operated on might be the key to improvement of outcome. Surgery is a major prognostic factor in our series (vs no surgery) and we assume the concept that among stage III patients, some should receive surgery whenever feasible at initial work-up. Pneumonectomy (particularly, right-sided) should be regarded with caution and remains an option in selected patients when adequate procedures are available and feasible.

In the future, PET CT could become a surrogate for the selection of patients to be referred for surgery: Schmuecking et al. [21] have shown that metabolic response after induction CRT, evaluated within 1 week following its completion, is highly predictive of pathological response.

5. Conclusion

In our study, surgery was feasible after induction CRT, particularly lobectomy, in PS 0—1 stage IIB (Pancoast)/III NSCLC patients. Pathological response to induction CRT was high and a major predictive factor of OS (necrosis >50% or pCR). Survival of resected patients was encouraging. A randomized trial is needed to determine whether induction CRT is superior to induction CT alone.

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References


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Appendix A. Conference discussion

Dr P. Goldstraw (London, U.K.): Given that your overall median survival is 2 years, the same as patients having no surgery at all, only chemoradiotherapy, given that your results are entirely in keeping with the results of the intergroup study and the EORTC study, why do you say a randomized prospective study is necessary? What grounds for such optimism do you have?

Dr M. Pruyt (Avignon, France): We just had a little group of 107 patients and it was a fact a retrospective study.

Dr Goldstraw: Well a little group of 107 patients is a big group. What encouragement do you get from the results of your 107 patients that lead you to think that you need 400 or 500 patients in a randomized prospective study?

Dr Pruyt: Because there is a big response of this range of tumor necrosis and we saw in the slides that the tumor necrosis is highly significant for the overall survival.

Dr Goldstraw: But your tumor necrosis rate, the complete pathological response rate, is inflated by including patient with microscopic residual disease, which is not complete pathological response.

Dr Pruyt: That is correct.

Dr J. Kudziole (Zakopane, Poland): Your results of patients with N0—N1 disease after induction therapy were no different than with N2 disease. Do you propose any restaging after chemoradiation? Is it necessary to restage these patients or is it not? There is an ongoing discussion whether to restage these patients. Your results show something else, that it is not necessary.

Dr Pruyt: Yes indeed.