Comparative prognostic features of stage IIIAN2 and IIIB non-small-cell lung cancer patients treated with surgery after induction therapy

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Abstract

Objective: Induction Therapy (IT) before surgery emerged as a widely used strategy for IIIAN2 and selected IIIB NSCLC patients. However, IT is associated with a possible increase in postoperative complications. Consequently, selection of patients with the best chances to benefit from combined treatment is mandatory. Methods: Study recorded demographics, treatment and outcome of consecutive patients treated with IT plus surgery for IIIAN2 or IIIB NSCLC. Survival was analysed by Kaplan-Meier and prognostic factors were analysed by log-rank and Cox regression. Results: From 1993 to 2003, 155 patients (IIIAN2 = 95/IIIB = 60) were treated. Complete resection was associated with a significant prolonged median survival both for IIIAN2 (20 vs 16 months, \(P = 0.05\)) and IIIB (20 vs 15 months, \(P = 0.02\)) patients. A lower risk of death for IIIAN2 patients was independently associated with postoperative mediastinal lymph node clearance (HR = 0.45, 95% CI [0.25–0.81], \(P = 0.009\)) and absence of postoperative complication (HR = 0.54, 95% CI [0.31–0.91], \(P = 0.02\)). Absence of blood vessel invasion only was identified as an independent predictor of a lower risk of death (HR = 0.27, 95% CI [0.12–0.59], \(P = 0.01\)) for stage IIIB patients. Conclusions: Besides similarities as the role of a complete R0 resection, treatment-related factors influence outcome of IIIAN2 patients while disease-related factors prevail on survival of IIIB patients, in whom the benefit of IT is unclear.

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1. Introduction

Surgical resection remains the cornerstone for the treatment of early stage of non-small-cell lung cancer (NSCLC). A surgical management of locally advanced NSCLC, namely stage IIIAN2 and selected IIIB, frequently remains technically possible. However, the 5-year survival for stage IIIAN2 and selected IIIB NSCLC patients managed with front-line thoracic surgery alone remains low and usually less than 15% [1]. Therefore, combined treatments including induction therapy (IT) (chemotherapy associated or not with radiation therapy) followed by thoracic surgery have been the subject of many clinical trials. These trials suggested a significant survival advantage favouring the combination of IT plus surgery vs a front-line surgery alone [2–5]. Nevertheless, these clinical trials are the butt of some criticism, especially due to a small number of patients [2,3] or methodological issues (incomplete reported results [4] and incomplete pathological mediastinal lymph node staging [5]). Thus, as stated by the International Association for the Study of Lung Cancer (IASLC) 2003 consensus, a definitive standard regarding IT has always to be reached [6].

Whereas a possible survival improvement related to IT before surgery raises hopes, a few studies highlighted an increased postoperative morbidity and mortality for patients undergoing such a combined treatment. Actually, while lobectomy after IT is associated with a postoperative mortality ranging from 2.4 to 8%, pneumonectomy should be considered as a high-risk surgical procedure as testified by a postoperative mortality of 9–11.3%, growing up to 23.9% for right pneumonectomy [7–10]. In summary, surgery and especially pneumonectomy following a preoperative IT is associated with a postoperative mortality which may overcome the positive effects regarding survival of such a multimodality treatment. Therefore, a selection of NSCLC patients who mostly benefit from a surgical approach after IT is needed. While comparable IT regimens are applied for stage IIIAN2 as well as for stage IIIB NSCLC patients, the aim of the present study was to assess the comparative prognostic features for longer survival for both these patients.
2. Patients and methods

2.1. Patients

All the patients treated at our institution by IT for a stage IIIAN2 or a stage IIIB NSCLC from 1993 to 2003 were included into the study. All the data were extracted from the computerised database of our institution. Clinical examination, fiberoptic bronchoscopy and chest, abdomen and brain computed tomographic scans were carried out systematically. A complementary examination by 18-FDG PET-scan was done since the last 2 years.

Any mediastinal lymph node greater than 10 mm in its shortest diameter was considered as pathologic. The mediastinal lymph node involvement was confirmed either pathologically after a cervical mediastinoscopy or functionally after demonstrating an 18-FDG uptake.

The initial TNM staging was done according to the Union Internationale Contre le Cancer classification [1].

The preoperative workup regarding respiratory and cardiac assessments was done accordingly to national guidelines [11].

2.2. Treatments

Chemotherapy drugs, number of cycles, adjunction of radiotherapy and grade III-IV toxicity were collected. Clinical response to IT was assessed using the WHO criteria on the same basis than the pre-treatment workup. Patients for whom local disease progression was suspected were considered as candidates for surgery only if a complete resection was thought to be possible. Re-mediastinoscopy was performed anecdotally. The extent of the performed lung resection was tailored on the intra-operative assessment of the residual disease. The surgical procedure was standardised according to actual standard regarding the pulmonary resection as well as the mediastinal lymph node dissection [11]. Operative morbidity and mortality were defined as any event occurring during the first 30 days following surgery or during the same hospitalisation. Postoperative complications were divided in minor and major complications. Major complications included prolonged stay or readmission to the intensive care unit, acute respiratory distress syndrome, broncho-pleural fistula, haemothorax, septic shock, myocardial infarction and severe heart failure defined using internationally available criteria. Postoperative treatment when appropriate was recorded.

2.3. Pathological assessment

Histological sub-classification was done according to the World Health Organisation classification [12]. Completeness of resection, mediastinal lymph node stations involvement and pathological features such as vascular or lymphatic invasion (blood vessel invasion), involvement of visceral pleura and tumour grade were reported using internationally available criteria. The pathological staging was equally done using the UICC classification. The downstaging was defined as a decrease in the postoperative pathological TNM stage when compared with the initial TNM stage. The mediastinal clearance was defined as a complete disappearance of a pathological mediastinal involvement.

2.4. Survival

Survival data were updated in November 2004. Overall survival was defined as the time between the start of IT and the date of last follow-up or any cancer-related and unrelated death. Progression-free survival was defined as the time between the start of IT and the date of the first sign of relapse. The site (local or general) of the first cancer relapse was collected.

2.5. Statistical analysis

Overall survival and progression-free survival were estimated using the product limit method of Kaplan-Meier and included the operative mortality. Factors potentially influencing postoperative complications were analysed by the Pearson’s $\chi^2$ and Fisher’s exact test. Kaplan-Meier log-rank and Cox regression analyses were used for univariate analyses. Proportional hazards regression (Cox model) was used to incorporate in the same model any explanatory variables with a $P$-value less than 0.20. Forward stepwise procedure and likelihood ratio tests were used to select the variables with the greatest prognostic value. A $P$-value less than 0.05 was considered as significant. The comparative impact of all the potential prognostic factors for survival was calculated using the above described methods for each stage (i.e. IIIAN2 and IIIB) of the disease. The statistical analysis was performed by using the SPSS V10.0 software package (SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Patients

Between 1993 and 2003, 204 patients including all stages of NSCLC were operated on after IT at our institution. In the same period, 155 patients received IT before surgery specifically because of a stage IIIAN2 ($n=95$) or IIIB ($n=60$) NSCLC. The demographical data of these patients are summarised in Table 1. Patients were classified as IIIB mostly in keeping with the presence of a T4 tumour ($n=55$) or a N3 lymph node involvement ($n=5$). Performance Status was 0 or 1 for all the patients.

3.2. Treatment

All the patients received platinum-based combination chemotherapy (Table 1). For stage IIIAN2 patients, the chemotherapy regimen was a doublet mainly based on a third generation drug (vinorelbine, $n=38$; docetaxel, $n=4$; paclitaxel, $n=19$; gemcitabine, $n=12$) and less frequently on older drugs (etoposide, $n=20$; other, $n=2$). Regarding stage IIIB, the chemotherapy was also a doublet based on a third generation drug (vinorelbine, $n=23$; docetaxel, $n=3$; paclitaxel, $n=3$; gemcitabine, $n=7$) or older drug (etoposide, $n=22$; other, $n=2$). Actually, one-third ($n=41$) of the patients also received a thoracic radiation therapy.
The median dose of radiation therapy was 45 Gy [30–60 Gy]. The median number of cycles for chemotherapy was 3 [1–6] without significant differences between stage IIIAN2 and IIIB.

After radiological assessment, there were 13 (8.4%) complete and 67 (43.2%) partial responses without significant differences between stage IIIAN2 and IIIB. As a result, the objective response rate was of 51%. In all, 67 patients (43.2%) showed a stable disease. Only few patients experienced a disease progression during IT (n = 8, 5.1%).

The details on the surgical procedure are given in Table 1.

<table>
<thead>
<tr>
<th>Socio-demographic characteristics</th>
<th>Stage IIIAN2 pts, N=95 (%)</th>
<th>Stage IIIB pts, N=60 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>80 (84.2)</td>
<td>52 (86.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>27 (28.4)</td>
<td>16 (26.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Histology (%ADC)</td>
<td>43 (45.3)</td>
<td>20 (33.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Induction therapy features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd generation Cx regimen</td>
<td>71 (74.7)</td>
<td>33 (56.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>≤ 3 Cycles Cx</td>
<td>81 (85.3)</td>
<td>49 (81.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Associated Rx</td>
<td>20 (21.1)</td>
<td>23 (38.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Haematological toxicity gr3–4</td>
<td>14 (14.7)</td>
<td>11 (18.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Non-haematological toxicity gr3–4</td>
<td>18 (18.9)</td>
<td>7 (11.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Overall response ratea</td>
<td>48 (50.5)</td>
<td>32 (53.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Surgical procedure features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomies</td>
<td>53 (55.8)</td>
<td>20 (33.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pneumonectomies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>15 (15.8)</td>
<td>19 (31.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Right</td>
<td>25 (26.3)</td>
<td>16 (26.7)</td>
<td></td>
</tr>
<tr>
<td>30 days complications</td>
<td>37 (41.1)</td>
<td>29 (48.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Severe complicationsb</td>
<td>15 (16.7)</td>
<td>13 (21.7)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ADC, adenocarcinoma; Cx, chemotherapy; Rx, radiotherapy.
a Radiological response rate.
b See text for details.

The median dose of radiation therapy was 45 Gy [30–60 Gy]. The median number of cycles for chemotherapy was 3 [1–6] without significant differences between stage IIIAN2 and IIIB.

After radiological assessment, there were 13 (8.4%) complete and 67 (43.2%) partial responses without significant differences between stage IIIAN2 and IIIB. As a result, the objective response rate was of 51%. In all, 67 patients (43.2%) showed a stable disease. Only few patients experienced a disease progression during IT (n = 8, 5.1%). The details on the surgical procedure are given in Table 1. There was significantly more pneumonectomies for stage IIIB than for stage IIIAN2 patients (67 vs 44%, P = 0.02). The overall operative mortality rate was 8.7% (Acute respiratory distress syndrome, n = 7; bronchial fistula, n = 2; myocardial infarction, n = 1; haemothorax, n = 1; acute heart failure, n = 1, pulmonary embolism, n = 1). In all, 38 (25.6%) and 27 patients (18.2%) experienced minor and major postoperative complications, respectively. Major complications were the following: bronchial fistula (n = 13), ARDS (n = 7), bleeding (n = 2), myocardial infarction (n = 2) and haemothorax (n = 2), septic shock (n = 1). Finally, 95 patients (61.3%) received a postoperative treatment with chemotherapy (n = 55) and/or radiation therapy (n = 81) without significant differences between stage IIIAN2 and IIIB.

3.3. Pathological assessment

Histological sub-types equally showed adenocarcinoma (n = 63, 40.6%) and spinocellular carcinoma (n = 62, 40%). The other pathological features of resected lung specimens were described in Table 2.

3.4. Survival

Only 6 (3.8%) patients were lost to follow-up. The median follow-up was 72 months. Median (MS), progression-free (PFS) and overall (OS) survivals were shown in Table 3. Factors influencing survival as a result of the univariate and multivariate analysis are given in Table 4. Comparative prognostic features of survival for stage IIIAN2 and IIIB patients are represented in Figs. 1 and 2.

4. Discussion

IT emerged as a widely used strategy for stage IIIAN2 and selected stage IIIB NSCLC patients. However, IT raises a dilemma with on the one hand a possible survival improvement related to preoperative IT, but on the other hand...
a parallel increase in postoperative complication. In turn, the main concern is how to select properly those patients with the best chances to benefit from such a combined treatment strategy. In the present study, achievement of a complete resection was associated with a significant prolonged survival both for stage IIIAN2 (MS of 20 vs 16 months, \( P = 0.05 \)) and IIIB (MS of 20 vs 15 months, \( P = 0.02 \)) NSCLC patients. In addition, a lower risk of late death for patients with stage IIIAN2 NSCLC was independently associated with the achievement of a postoperative mediastinal lymph node clearance (HR = 0.45, 95%CI [0.25–0.81], \( P = 0.009 \)) and the absence of postoperative complication (HR = 0.54, 95%CI [0.31–0.93], \( P = 0.02 \)). Regarding patients with stage IIIB NSCLC, the absence of blood vessels invasion only was identified as an independent predictor of a lower risk of death (HR = 0.27, 95%CI [0.12–0.59], \( P = 0.01 \)).

The reported survival for patients treated with IT widely varies throughout the studies, from 18 to 43% [3,4,13], and could be related in part to the inclusion of stage IIIB patients. Therefore, a 3-year survival of 28.2 and 27.3% for herein reported stage IIIAN2 and IIIB patients, respectively, is consistent with the literature. The present study highlights some putative prognostic features of stage IIIAN2 and IIIB patients. After IT, those patients with an incomplete resection experienced a significantly higher risk of death when compared with patients showing a complete resection (HR from 3.2 to 3.8) [13–16]. Therefore, a surgical procedure after IT without a reasonable assurance to reach a complete resection (i.e. R0) should be avoided for stage IIIAN2 as well as for stage IIIB NSCLC patients. Besides complete resection, downstaging recently emerged as a predictor for longer survival for NSCLC patients with stage IIIAN2 as well as IIIB managed with IT plus surgery [13,15–20]. However, it is still unclear if achievement of a complete mediastinal clearance (i.e. postoperative pN0 stage), as used in the present study, provides a greater survival benefit over a downstaging (i.e. decrease from preoperative pN2 to a postoperative pN0 or pN1 stage). Both these two prognostic factors have been used throughout previously published studies and a large prospective trial would be useful to determine the target to be reached by IT. In addition to complete resection or mediastinal clearance, survival of stage IIIB NSCLC patients was also influenced by the presence of a vascular or lymphatic blood vessel invasion. In fact, a 1.8–13 significant increased in the risk of death has already been related to the presence of blood vessel invasion for NSCLC patients treated with surgery alone [21]. Therefore, the poor prognosis related to the presence of a blood vessel invasion justified in part the combination of a systemic treatment with surgery. Unfortunately, the present results demonstrated that blood vessel invasion remains a poor prognostic factor for stage IIIB patients, in spite of the administration of an IT. In consequence, a possible inability of IT to challenge the shorter survival associated with the presence of a blood vessel invasion.
vessel invasion might question the use of a preoperative IT for stage IIIB NSCLC patients potentially candidate for a front-line surgery.

This study aimed to report daily practice results. However, while stage IIIAN2 patients represent a homogeneous group, heterogeneity of stage IIIB patients is greatest (according to the UICC classification) and results reported for this group have to be prospectively confirmed. Hitherto, only few randomised trials evaluating the benefit of surgery after IT for stage IIIAN2 or stage IIIB patients are still open to date, sometimes closed early due to a poor accrual [22]. Thus, in spite of possible bias, assessment of the benefit related or not to IT through daily practice results is of interest.

As specified before, the benefit of surgery after IT might be balanced by an increasing rate of postoperative complications as reported in the present study for stage IIIAN2 patients. In this context, the results of two major trials, intergroup trial 0139 and EORTC 08941, were recently reported. The intergroup 0139 trial randomised IIIApN2 patients (n=396) between surgery vs radiotherapy, after an IT regimen based on chemo-radiotherapy. Although, progression-free survival was longer for patients in the surgical arm, there was no significant difference between the two arms regarding overall survival (HR = 0.87, 95%CI [0.70-1.10], P = 0.24) [23]. The EORTC 08941 trial (n=570 patients) randomised responding IIIApN2 patients between surgery vs radiotherapy, after an IT regimen based on chemotherapy alone. No progression-free or overall survival difference appeared between the two arms (HR=1.06, 95%CI [0.84-1.35], P=ns) [24]. Although surgery after IT for stage IIIAN2 and III NSCLC patients might still remain an option, previous results combined with the present study highlight the need to avoid (i) the risk of an incomplete resection, (ii) a postoperative mediastinal lymph node involvement and (iii) the risk of postoperative complications. As a first consequence, a strict preoperative workup is needed. As a second consequence, a rigorous assessment of the preoperative status of mediastinal lymph node is also needed. Regarding this issue, small phase II studies based on invasive re-mediastinoscopy [25] or non-invasive PET scan [26] provided interesting results, but further large prospective studies are mandatory. Finally, postoperative complications should be controlled probably through, firstly, a rigorous selection of patients candidate for surgery[10], and secondly, an improvement of surgical procedures especially regarding the risk of right pneumonectomies. Sleeve lobectomy should perhaps be preferred whenever feasible and bronchial strump reinforcement has to be done to prevent occurrence of bronchial fistula.

5. Conclusion

The present study suggests some similarities as the pivotal role of a complete R0 resection for stage IIIAN2 and IIIB patients. Further analysis suggests that treatment-related factors strongly influence the outcome of stage IIIAN2 patients, since longer survival may be achieved when IT combines mediastinal lymph node clearance with low-related toxicity. In contrast, disease-related factors prevail on survival of stage IIIB ‘surgical’ patients, in whom the benefit of IT is unclear. These features are suggested to be relevant indicators to support decision making in a multi-disciplinary cancer team.

References


