The role of chemoradiotherapy in the treatment of stage III non-small-cell lung cancer

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Introduction

Although mortality of lung cancer in men among the countries of the European Union is steadily decreasing, there is still an increasing mortality among women, and as a consequence the overall rate of lung cancer-related deaths has not been declining in Europe [1, 2]. Thus, the development of optimized treatment approaches in lung cancer patients remains an urgent issue. Today, non-small-cell lung cancer (NSCLC) histopathologies represent the vast majority, representing >85% of all lung cancer patients [3]. Stage III NSCLC, the locally advanced tumor stage, has offered the best chances for possible therapeutic innovations and improvements by the introduction of interdisciplinary, combined modality treatment strategies [4, 5]. With systemic relapses being a major problem in this patient subgroup, combination chemotherapy has emerged as an integral part of the overall treatment management [6, 7]. Combinations of radiotherapy and platinum-based chemotherapy have consequently been proposed as standard of care for the vast majority of these patients in stage III [5, 7, 8]. Surgery plays a generally accepted role in only a small group of patients with minimal or operable (‘surgical’) stage III disease [6, 8–10]. In 2000, we reviewed the literature for a comprehensive overview on combined modality treatment of NSCLC [11]. In the following paper, we will give a short update on important new developments since the year 2000 in multidisciplinary treatment approaches, including both combination chemotherapy and radiotherapy. Special focus has been on newer drug combinations in this setting, innovations in radiotherapy application and concurrent treatment protocols. New findings dealing with the overall role of surgery in this setting will be critically discussed.

Methods

The current literature on the subject of this manuscript was reviewed by performing a literature search starting from January 2000 up to 15 June 2004. We included an internet-based literature search via the PubMed database by combining the items of ‘chemoradiotherapy and NSCLC and stage III’, ‘chemotherapy and radiotherapy and NSCLC and stage III’, ‘chemoradiation and NSCLC and stage III’ and ‘combined modality therapy and NSCLC and stage III’. Furthermore, we searched for trials on this topic that had been presented at major international oncological conferences such as the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Conference on Clinical Oncology and World Conference on Lung Cancer between 2000 and 2004. We included reported analysis from phase III trials as well as from selected important phase II investigations over this time interval. The emphasis was on important new data since 2000, and therefore we have included older studies only into this analysis if either no comparable new investigation is currently available and the implications from these studies are of major importance for the current treatment management, or if the results of these trials have been recently updated in the stated time period.

Results

To bring the recent literature into a broader perspective, we briefly summarize the main findings from our 2000 review as a background for further analysis.

Major statements from the last overview presented in 2000

The 2000 review [11] concluded that combination therapy of chemotherapy and radiotherapy was the standard of care for stage III NSCLC. At that time, data from randomized trials comparing radiotherapy alone versus combinations of chemotherapy and radiotherapy had shown clearly that these combinations were superior concerning long-term results. Induction chemotherapy prior to radiation was able to reduce systemic relapse outside the brain. When chemotherapy was given concurrently with radiation, it was able to reduce local relapse and thus made radiation more effective locally. This improvement in local control translated into a significant survival benefit for the patients. However, concurrent application of chemotherapy and radiotherapy was considerably more toxic, but overall was acceptable in this respect compared with the sequential scheduling. The overall role of surgery at that time was debatable, but was under evaluation in large randomized trials (e.g. Intergroup 0139). There were insufficient data for an individualization of treatment decisions based on prognostic factors or biological markers.

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Table 1. Adjuvant chemotherapy in NSCLC: randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Patients</th>
<th>Regimen</th>
<th>Median 5-year SR (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI [12]</td>
<td>I–IIIA</td>
<td>603</td>
<td>MVP</td>
<td>N/A</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>606</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IALT [13]</td>
<td>I–III</td>
<td>935</td>
<td>PE/PNav/PVbl/PV</td>
<td>44.5</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>932</td>
<td>–</td>
<td>40.4</td>
<td>–</td>
</tr>
<tr>
<td>NCIC [14]</td>
<td>I–II</td>
<td>243</td>
<td>PNav</td>
<td>69</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>239</td>
<td>–</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>CALGB II</td>
<td>173</td>
<td>Pac/Carbo</td>
<td>71*</td>
<td>&lt;0.03</td>
<td></td>
</tr>
</tbody>
</table>

*Four-year SR.

SR, survival rate; ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Trial; NCIC, National Cancer Institute of Canada; CALGB, Cancer and Leukemia Group B; MVP, mitomycin/vindesine/cisplatin; P, cisplatin; E, etoposide; Nav, navelbine; Vbl, vinblastine; Pac, paclitaxel; Carbo, carboplatin; N/A, not available.

Chemotherapy in combined modality protocols: implications from recent adjuvant trials

Since 2000, the results from four major randomized trials looking at the role of postoperative combination chemotherapy following complete resection of NSCLC have been published or reported [12–15] (Table 1). Only the first two of these studies included subgroups of stage III in the patient selection. While the first trial could not substantiate a significant survival benefit for adjuvant chemotherapy, there was a clear trend for a prolongation of event-free survival in the group that received adjuvant mitomycin C, vindesine and cisplatin (MVP) chemotherapy [12]. Stage III disease was included in this study (about one-third of the patients), but no subgroup analysis was available. There were arguments against the MVP protocol used in this trial because of peri- or postoperative toxicities, especially in the combination of sequentially administered postoperative radiation therapy.

The second trial to be analyzed was the large, multinational International Adjuvant Lung Trial (IALT) [13]. This megatrial included >1800 randomized patients and showed at 5 years a significant overall survival benefit of 4.1% for adjuvant cisplatin-based combination chemotherapy and a progression-free survival benefit of 5.1%. Moreover, this effect was independent of different covariates such as stage (one-third of patients included had stage III disease), histology, age and gender. The results of this trial favor the postoperative administration of adjuvant cisplatin-based combination chemotherapy in completely resected stage III NSCLC [13].

These findings have major implications on the treatment strategy for stage III NSCLC, and it seems advisable to include a systemically active cisplatin-based chemotherapy into the management of stage III disease. This intervention leads to a significant improvement in systemic control outside the brain, similar to that observed with combinations with radiotherapy.

Two further randomized trials with adjuvant chemotherapy in early disease have recently been presented at the ASCO 2004 conference. Both trials showed significantly improved survival results with the administration of postoperative chemotherapy, but neither included a subset of stage III patients [14, 15].

A randomized trial of postoperative chemoradiotherapy in stage II and III patients did not show a significant impact on survival outcome [16]. This trial, performed by Eastern Cooperative Oncology Group, has been criticized for the reduced ‘systemically active’ chemotherapy doses included in this trial setting based on the postoperative concurrent chemoradiotherapy regimen.

New data on concurrent chemoradiation since 2000

In recent years there has been further evidence from randomized phase III trials or prospective randomized trials favoring a concurrent administration of chemotherapy and radiotherapy over a sequential schedule [17–20] (Table 2). It should be noted that within these chemoradiation trials, patients with inoperable stage IIIA and IIIB were included and no pathological staging of the mediastinum was recommended prior to inclusion. This translates into a rather different patient selection within these studies compared with those that have a detailed surgical staging of the mediastinum. However, while three of the four randomized trials found increased survival duration for the concurrent chemoradiation arms [17–19], not all trials could substantiate a significant survival benefit for the simultaneous administration of chemotherapy and radiation [19, 20]. Most of these trials reported concern about the observed toxicity of the more intensive chemoradiation protocols. It could be that learning effect within the participating cooperative groups and treatment centers is responsible for differences in toxicities. In addition, it may be speculated that

Table 2. Sequential versus concurrent chemotherapy and radiotherapy: randomized trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage</th>
<th>Patients</th>
<th>Regimen</th>
<th>Median</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zatloukal [17]</td>
<td>IIIA</td>
<td>102</td>
<td>PNav+RT 60 Gy (seq)</td>
<td>16.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Fournel [18]</td>
<td>IIIA</td>
<td>104</td>
<td>PNav+RT 66 Gy + PNav (seq)</td>
<td>13.8</td>
<td>&lt;0.41</td>
</tr>
<tr>
<td>Curran [19]</td>
<td>II–III</td>
<td>610</td>
<td>PNav ×5+RT 60 Gy (seq)</td>
<td>14.6</td>
<td>–</td>
</tr>
<tr>
<td>Huber [20]</td>
<td>IIIA</td>
<td>104</td>
<td>Pac/Carbo ×2+Pac + RT 60 Gy</td>
<td>18.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>115</td>
<td>Pac/Carbo ×2+RT 60 Gy</td>
<td>14.1</td>
<td>–</td>
</tr>
</tbody>
</table>

P, cisplatin; Nav, navelbine; RT, radiotherapy; seq, sequential; con, concurrent; E, etoposide; b.i.d., twice daily; Pac, paclitaxel; Carbo, carboplatin; NS, not significant.
The second trial was a randomized comparison of their piloted showed equal efficacy, but revealed differing toxicity profiles. Current chemoradiation, randomized phase II setting [24] at different new drug combinations in an induction plus concurrent chemoradiation is another alternative therapy the administration of induction chemotherapy prior to definitive upfront chemoradiation. The preliminary analysis was presented at the 2004 ASCO conference [25]. Although there was a 2.5-month increase in survival in the arm receiving induction treatment, this difference was not found to be statistically significant. It may be that the number of patients was too small to answer this important question. An unexplained finding of that study was the remarkably poor survival results in the upfront definitive chemoradiation arm in comparison with prior Cancer and Leukemia Group B (CALGB) studies. The authors speculated that the chosen concurrent chemotherapy combination in their trial (with weekly carboplatin and paclitaxel) may not have been the optimal choice to achieve adequate systemic control of disease. The weekly administration schedule may have been responsible, but also the role of carboplatin as a substitute to cisplatin within concurrent chemoradiation protocols is not widely accepted based on the currently available clinical data [26].

New data on high-dose conformal radiotherapy or other new radiotherapy techniques

With rapid innovations in new radiation planning techniques and the possibility of delivering conformal high-dose radiation protocols, there has been considerable progress in the development of high-end radiation protocols. In recent years, there have been a number of radiotherapy pilot trials aimed at radiation dose-finding and the evaluation of toxicity–efficacy ratios in this setting (Table 4) [27–33]. Local control in these high-dose studies has been reported to be improved, but a significant effect on survival outcome has yet to be established. In order to combine local control with improved systemic control, different clinical research groups have consequently tried to combine either induction chemotherapy or concurrent chemotherapy application with a higher-dose radiation schedule. Preliminary data from these phase II/III trials have been reported and compare favorably with historical controls in the same disease stages. No randomized comparison testing this strategy against conventionally dosed and fractionated chemoradiation protocols is currently available.

Another promising approach has been the development of hyperfractionated accelerated radiation (HART) schemes. So far, only one randomized trial of induction chemotherapy followed by HART versus standard single fractionated thoracic radiotherapy has been reported [34]. Unfortunately, this trial was terminated early due to slow patient accrual, but


<table>
<thead>
<tr>
<th>No. patients</th>
<th>Chemotherapy (mg/m²) (P 80+)</th>
<th>RT (66 Gy) + chemotherapy (mg/m²)</th>
<th>RR (%)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>Gem 1250: days 1, 8, 22 and 29</td>
<td>Gem 600: days 43, 50, 64 and 71</td>
<td>74</td>
<td>18.3</td>
</tr>
<tr>
<td>58</td>
<td>Pac 225: days 1 and 22</td>
<td>Pac 135: days 43 and 64</td>
<td>67</td>
<td>14.8</td>
</tr>
<tr>
<td>55</td>
<td>Nav 25: days 1, 8, 15, 22 and 29</td>
<td>Nav 15: days 43, 50, 64 and 71</td>
<td>73</td>
<td>17.7</td>
</tr>
</tbody>
</table>

*aAll patients received P 80 mg/m² on days 1, 22, 43 and 64 and radiotherapy 66 Gy (2 Gy per fraction) starting on day 43. P, cisplatin; RT, radiotherapy; RR, response rate; OS, overall survival; Gem, gemcitabine; Pac, paclitaxel; Nav, navelbine.
Modern functional imaging and its implications for the future

Positron emission tomography (PET) scanning is becoming more and more available as a functional imaging method at different European treatment institutions. This tool has been employed as a staging technique for both systemic dissemination and the mediastinal lymph node involvement [38–40]. Another possibility may be its inclusion during the course of treatment as a method to monitor mediastinal downstaging following induction therapy (either chemotherapy or chemoradiotherapy) [40, 41]. Its impact, however, may lie in its ability to guide individual radiation treatment planning within more and more sophisticated higher-dose conformal radiation techniques (e.g. in the form of PET-computed tomography) [42]. However, a final evaluation of this new technique remains to be determined in larger clinical settings.

Trimodality treatment design

Within recent years, three large randomized trials have looked at the combination of preoperative chemoradiation followed by surgery in subsets of patients with stage III disease [21, 43–45] (Table 5). The North American Intergroup 0139 trial was presented both at ASCO 2003 and at International Agency for the Study of Lung Cancer (IASLC) Conference 2003 with updated survival results [21, 43]. The patient selection of this trial included mediastinoscopically/pathologically proven IIIA (N2) disease. Randomization was either to induction chemoradiation followed by surgery and consolidation chemotherapy or to chemoradiation with boost radiotherapy followed by consolidation chemotherapy (Table 5). The current analysis substantiated a small, statistically non-significant 5-year survival improvement of 3% for the inclusion of surgery [21, 43]. On the other hand, progression-free survival was significantly improved by surgery. The background of these unequivocal findings for survival may be a problem originating from perioperative toxicity with acute respiratory distress syndrome in some patients, leading to a cross-over in the survival curves during the first year of the study.

The data from this study could be interpreted in two ways. There is a measurable benefit of surgery in the progression-free survival of the patients and this has important implications on the patients’ quality of life and should be a strong argument for the role of surgery in this setting, at least for a selected group of patients. However, overall survival and cure rate are not inferior with a bimodality-only treatment approach.
One could speculate that some patients (a defined subset) are already definitely cured by a concurrent chemoradiation protocol, and surgery may not add to the overall survival prognosis in this patient group. Currently, we do not have data on how to define clearly these prognostic subgroups. In the future, it should be an important clinical research strategy to identify these patient subsets by any possible means (e.g. clinically, with functional imaging, guided by translational research). A further important result of this large multicenter randomized trial was the finding that trimodality protocols are safe, and show acceptable toxicity profiles in the hands of experienced multidisciplinary treatment teams.

This could be further underlined by the study from the West German Cancer Centre Cooperative Group [44]. This multicenter German cooperative group aimed at the small but well defined subset of patients with operable IIIA disease (‘minimal IIIA’). Based on the background that the majority of European centers within recent years performed upfront surgery in this small subgroup of patients, their trial tested an induction chemotherapy plus concurrent chemoradiation protocol followed by surgery versus a local treatment-only approach (surgery followed by adjuvant radiotherapy) in patients without multilevel or clearly bulky N2 disease at mediastinoscopy. Although this trial had to finish patient accrual early after 110 randomized patients because of the results from the IALT investigation, the current analysis favors the survival results of the trimodality arm until 36 months [44]. However, the observed survival results can only point to a trend, and do not approach statistical significance based on the too small number of randomized patients. The detailed toxicity analysis of this study did not show a significant increase of perioperative morbidities or mortalities following the induction protocol. Another important finding of this study is the clear trend for more organ sparing surgery following a bimodality induction. The multimodality arm had only half the number of pneumonectomies compared with the upfront surgical arm. These data point to a possible downstaging effect of the bimodality induction protocol. Further interesting analysis will come from the data on brain relapse-free survival in both arms, as the combined-modality arm had prophylactic cranial irradiation included in the treatment protocol.

The third study was presented at the 2004 ASCO conference [45]. The German Lung Cancer Cooperative Group investigated the different timing of radiation therapy in the trimodality setting, given either preoperatively as part of the induction therapy or postoperatively as locoregional consolidation treatment [45]. The preliminary analysis of this large multicenter German trial could not substantiate significant differences in overall or progression-free survival between the two arms. However, the absolute 3-year survival rate seems to be slightly higher in the arm with preoperative radiation therapy. A longer follow-up may give more detailed conclusions about the long-term outcome of the included patients.

Criticism of this trial has arisen based on the following background. The included weekly carboplatin and vindesine regimen during chemoradiation has never been proven to be an active (concurrent) chemoradiation protocol. All patients received radiation therapy, either preoperatively or postoperatively; therefore, the overall role of radiation in this stage group cannot be defined with this trial design. The patient selection used in this randomized trial defined a very heterogeneous patient population, from early, minimal N2 disease to locally advanced IIIIB patients. This heterogeneity may make the final conclusions from this study difficult to transfer to other, more selected patient populations. Most importantly, the toxicity analysis of this trial could not substantiate any major difference in perioperative mortalities or mortalities between induction chemotherapy or induction chemoradiation. This argument had always been raised against intensive and complex treatment protocols in the preoperative setting.

Besides these three randomized studies, there have been further prospective phase II investigations reported within recent years that looked at the possible improvement of such intensive trimodality protocols [46–54] (Table 6). The preliminary data from these phase II trials showed promising

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Table 5. Randomized trials including trimodality treatment arms

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Stage</th>
<th>Treatment</th>
<th>PFS (months)</th>
<th>3-year SR (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albain [43]</td>
<td>429a</td>
<td>IIIA (N2)</td>
<td>PE ×2 + 45 Gy + S + PE ×2</td>
<td>14.0</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PE ×2 + 61 Gy + PE ×2</td>
<td>11.7</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Thomas [45]</td>
<td>558b</td>
<td>min IIIA to adv IIIB</td>
<td>PE ×3 + 45 Gy b.i.d./Carbo Vin + S ± 24 Gyc</td>
<td>10</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Eberhardt [44]</td>
<td>112c</td>
<td>min IIIA</td>
<td>PE ×3 + 54 Gy ± 14.4 Gy</td>
<td>10</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S + 50</td>
<td>29</td>
<td>38</td>
<td>0.16</td>
</tr>
</tbody>
</table>

aData on 392 patients.
bData on 526 patients.
cAdditional dose on patients with R1/R2 resection.
dData on 106 patients.

PFS, progression-free survival; SR, survival rate; P, cisplatin; E, etoposide; S, surgery; NS, not significant; min, minimal; Adv, advanced; b.i.d., twice daily; Carbo Vin, carboplatin vindesine; PCI, prophylactic cranial irradiation.
survival results when newer chemotherapy regimens were included [51, 52, 54]. Moreover, toxicity profiles could be further improved with these modern third-generation platinum combinations, and this represents a strong argument in multimodality protocols where treatment compliance is an important prerequisite for efficacy [51, 52, 54]. However, it has not been established clearly whether these newer combinations represent a significant survival benefit in comparison with the standard cisplatin/etoposide regimen. There have also been detailed reports about the toxicity profiles of these aggressive multimodality approaches to locally advanced NSCLC [55, 56].

For superior sulcus tumors, multicenter phase II trials have been carried out with these trimodality protocols, and for these selected subgroups of stage III disease this management has emerged as the new standard of care [57, 58].

Treatment of elderly patients
At the moment there is no clear evidence for why elderly patients should not be given intensive bimodality (chemoradiotherapy) regimen in stage III disease. A detailed retrospective analysis could not find negative effects, and also a survival benefit was observed in this elderly patients group for intensive chemoradiation treatment [59]. However, co-morbidity profiles of the patients should be respected when deciding on the individual treatment strategy, and patients with a performance status of ≥2 should be managed with caution.

Patient selection
Comorbidity profiles
For trials reported in patient populations of stage III, it should be a prerequisite to describe in detail the comorbidity profiles of the patients. This has not always been the case for multimodality trials in the past. However, when publishing these data, it should become standard to provide comprehensive information on the existing comorbidities of the selected study population at the time of accrual.

Risk factor and prognostic factor analyses
To adequately select patients for different therapeutic approaches such as bimodality or trimodality treatment protocols, we need more detailed data on risk groups for developing toxicities, or prognostic factors [60]. So far, no significant biological or molecular prognostic factors in stage III disease have been established.

Critical end points for clinical research in this setting
Overall survival is still the major end point by which to evaluate different multimodality strategies. Progression-free survival is another important parameter to be taken into account, and this is influenced by local control as well as systemic relapses. Its implications on patients’ quality of life can only be speculated on, but should be scientifically analyzed. Cumulative brain relapse has become a major concern and should be reported for the patient population with stage III [61, 62]. Toxicity is a continuing issue with modern aggressive bimodality and trimodality protocols. Organ preservation or organ-sparing surgery due to downstaging effects should be looked at in more detail. Long-term toxicity reporting for both bimodality and trimodality treatments should be encouraged.

Discussion
Evidence from phase II investigations
More and more European treatment centers have developed structured programs with bimodality chemoradiation protocols or trimodality regimen for stage III NSCLC. Therefore, in recent years, more and more experience with complex interdisciplinary management of these patients has been gained both in single institutions and also in multicenter cooperative

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage (no. patients)</th>
<th>Chemotherapy</th>
<th>CcRTx (Gy)</th>
<th>Med OS (months)</th>
<th>5-year SR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunenwald [46]</td>
<td>IIIB (40)</td>
<td>P/5-FU/Vbl</td>
<td>40 b.i.d.</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>Ichinose [47]</td>
<td>IIIB (27)</td>
<td>P/UFT</td>
<td>40 qd</td>
<td>NA</td>
<td>56a</td>
</tr>
<tr>
<td>Machty [48]</td>
<td>IIIA (53)</td>
<td>P/E or Carbo/Pac</td>
<td>45–54 qd</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>DeCamp [49]</td>
<td>IIA/IIIB (78/27)</td>
<td>P/Pac</td>
<td>NA b.i.d.</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Katayama [50]</td>
<td>IIA/IIIB (14/8)</td>
<td>P/Doce</td>
<td>40 qd</td>
<td>NYR</td>
<td>66b</td>
</tr>
<tr>
<td>Ahn [51]</td>
<td>IIIA (31)</td>
<td>NA</td>
<td>NA</td>
<td>19</td>
<td>37.2</td>
</tr>
<tr>
<td>Gauler [52]</td>
<td>IIA/IIIB (24/40)</td>
<td>P/Pac</td>
<td>45 b.i.d. (P/E)</td>
<td>25</td>
<td>47b</td>
</tr>
<tr>
<td>Trodella [53]</td>
<td>IIA/IIIB (57/35)</td>
<td>Carbo or P/5-FU</td>
<td>50.4 qd</td>
<td>17.2</td>
<td>15</td>
</tr>
<tr>
<td>Freidel [54]</td>
<td>IIIA/IIIB (31/83)</td>
<td>Carbo/Poc</td>
<td>45 b.i.d.</td>
<td>22</td>
<td>57 (3 yr SR)</td>
</tr>
</tbody>
</table>

aTwo-year SR; b3-year SR.
CcCTx/RTx, concurrent chemoradiotherapy; OS, overall survival; SR, survival rate; P, cisplatin; 5-FU, 5-fluorouracil; Vbl, vinblastine; bid, twice a day; NA, not available; UFT, uracil/tegafur; qd, once daily; E, etoposide; Carbo; carboplatin, Pac, paclitaxel; Doce, docetaxel; NYR, not yet reached.
trials groups. The driving force of these different phase II trials has been to introduce more modern chemotherapy protocols into this setting, improve chemoradiation protocols, develop better supportive treatment measures and thus to reduce the overall toxicity of these complex therapies while in parallel making the management more effective. In the future, these datasets should be joined to provide more evidence on prognostic or predictive factors for different therapeutic strategies. These would help us to individualize approaches in our patients and to improve the overall outcome of this disease.

Evidence from phase III investigations

The major phase III investigations in stage III NSCLC have been the Radiation Therapy Oncology Group trial on concurrent versus sequential chemotherapy and radiotherapy, and the Intergroup 0139 trial looking at the role of surgery in stage IIIA (N2) disease [19, 21, 43]. These trials have further established concurrent chemoradiotherapy protocols as an accepted standard of care for stage III NSCLC.

However, surgery is still adequate in early and operable IIIA disease. There are clear arguments favoring the surgical approach following induction chemoradiotherapy for selected subgroups of stage IIIA based on the improved progression-free survival in Intergroup 0139 [21, 43].

The role of surgery in more advanced IIIA or selected IIIB disease remains to be established and is currently a matter of investigation (ESPATU; Table 7). The optimal induction therapy approach, either induction chemotherapy or induction chemoradiotherapy, prior to definitive surgery has not been finally established. The large German Lung Cancer Cooperative Group trial has given preliminary, but not sufficient, evidence concerning this important question based on its trial design [45]. Therefore, a new North American Intergroup trial has been planned to start accrual shortly, which will test preoperative chemotherapy versus preoperative chemoradiation in stage IIIA (N2). The design of this trial has been finished and has already been presented at the 2004 ASCO conference (Table 7). The CALGB trial looking at the role of induction therapy prior to concurrent chemoradiation has reported unequivocal findings [25]. Although the median survival was longer following the administration of an induction therapy, statistical significance was not reached within this trial. Furthermore, the survival results were disappointing in both arms of the study, probably indicating that the patient selection or the chosen chemotherapy protocol were responsible for this finding. Further evidence from prospective randomized trials has given first hints that downstaging effects, similar to that seen in other solid tumors, leading to organ sparing surgery or organ preservation, seem to be a new important and future end point of clinical research [44]. Reduction of toxicity profiles for multimodality protocols in stage III disease seems to be established by the new third-generation combination chemotherapy regimen [24]. However, the long-term outcome of treatment with these regimen remains to be seen.

Evidence from meta-analysis

Since 2000, no new data from meta-analyses on combined modality therapy in stage III have been published. There will shortly be two meta-analyses based on individual patient data, one looking at the effect of adjuvant chemotherapy following complete resection in NSCLC, and the other at the role of neo-adjuvant chemotherapy in resectable NSCLC. Findings from the stage III subset of these investigations will clearly have major implications on the design of future trials projects in stage III NSCLC. Local treatment only arms will not be an adequate reference arm within future trials projects. Updates of individual treatment guidelines in the different countries and by different medical societies are pending and will be performed shortly. Based on the remarkable heterogeneity of the patient population in stage III NSCLC, treatment individualization based on risk profiles, biological correlates or prognostic factor analyses will become more and more indicated.

Ongoing trials with new treatment principles and still open issues

Different study groups or international industry-sponsored trials are currently evaluating the role of new molecular targeted drugs within the interdisciplinary approach to stage III NSCLC (Table 7). The first results with these innovative agents will probably be available for the EGFR tyrosine
kinase inhibitors that are currently tested as a maintenance treatment following the administration of bimodality or trimodality protocols (Table 7). Other major phase III trials in stage III that are currently ongoing or are awaited to be reported, and that include treatment arms with chemoradiation, are summarized in Table 7.

Summary and conclusions

Any therapeutic management of patients with stage III NSCLC has to take into account the marked prognostic heterogeneity and the individual comorbidity profiles within these patient groups. Unfortunately, only a few prospectively randomized investigations have been reported within recent years that may have an influence on evidence-based treatment guidelines. Therefore, within this time period, only a few general principles of care could be established for the interdisciplinary approach to these patients:

(i) a combination of chemotherapy and radiotherapy should be the minimum requirement of management;

(ii) concurrent application of chemotherapy and radiation therapy is accepted as an optimal therapeutic strategy and should be the first choice in patients with good performance status and an adequate comorbidity profile, unless contraindications to these more toxic protocols exist;

(iii) inclusion of chemotherapy into any combined modality protocol for stage III is generally advisable;

(iv) surgery as part of an interdisciplinary treatment protocol is standard of care in the small subset of patients with initially operable stage III;

(v) surgery following induction therapy is possible in experienced hands/treatment groups, but its overall role still is debatable and not definitely accepted in patients with initially inoperable stage III;

(vi) radiation doses, conformal application of radiation and optimal fractionation schemas are as yet not well defined;

(vii) optimal chemotherapy combinations are not well defined;

(viii) administration of complex bimodality or trimodality treatment protocols requires dedicated, experienced and functioning multidisciplinary treatment teams to guarantee high quality of care as well as an adequate handling of side-effects; and

(ix) no molecular prognostic factor has up to now been established for these locally advanced stage subsets.

Further results of important phase III trials in stage III are awaited and may influence our treatment strategies and portfolio in the future.

References


