Patients with early stage non–small cell lung cancer (NSCLC) treated with single modalities are at high risk for local regional recurrence and distant relapse. The aim of decreasing both failure patterns has led both clinicians and investigators to evaluate the potential benefit of combined chemoradiotherapy (CTRT) given either concurrently or sequentially. Sequential CTRT should allow full doses of each modality to be given without the additional toxicity that occurs with concurrent therapy. Induction chemotherapy can reduce tumor volume, allowing smaller field radiotherapy, with less normal tissue toxicity, and potentially permitting higher doses of both modalities. Furthermore, tumor reduction with chemotherapy could reduce radioresistant hypoxic areas present in bulky tumors (1). There are three main settings where the use of sequential chemoradiotherapy in early stage NSCLC has been explored: as adjuvant therapy after resection, as neoadjuvant chemotherapy and surgery followed by radiotherapy, and in unresectable stage III disease. The available data pertaining to these three potential applications of sequential CTRT in the management of early stage NSCLC, with a focus on stage III disease, are herein reviewed.

**Adjuvant: Sequential Chemotherapy-Radiotherapy Following Surgery for Stages I to III**

The largest meta-analysis, which included stages I to III, examined six trials of cisplatin-based chemotherapy followed by postoperative radiotherapy (PORT) after complete surgical resection, with a nonsignificant survival gain for sequential postoperative CTRT over surgery and PORT alone. In a planned subgroup analysis, the relative survival benefit with sequential postoperative CTRT tended to be better ($P = 0.07$) for stage III patients than for stages I or II (2). Several subsequent reports have presented negative findings for PORT alone. A meta-analysis (recently updated) of PORT alone without chemotherapy in 2,128 patients revealed a 7% survival detriment at 2 years and 6% at 5 years compared with no PORT, particularly in stages I, II, N0, and N1, with no effect in stage III (3, 4). A randomized trial of 104 patients, which was stopped early, suggested a possible survival advantage with PORT for stage I patients and was included in the meta-analysis update but did not alter the original conclusions (4, 5). A subsequent trial in stages II, IIIA, and IIIB confirmed the failure of PORT to increase overall survival (6). Attempts to explain the poorer survival have argued that inferior radiotherapy techniques were used and that some trials were underpowered (7). More recently, a trial randomized resected patients with stage II or IIIA disease to thoracic radiotherapy or concurrent CTRT (8). There was no difference in survival, although concurrent chemoradiotherapy is considered a standard approach in more advanced disease. The Adjuvant Lung Cancer Project Italy study randomized patients to three courses of triplet chemotherapy with investigator choice to give radiotherapy after the chemotherapy; there was no survival difference (9). However, a somewhat larger study (the International Adjuvant Lung Trial) that allowed a variety of cisplatin regimens followed by radiotherapy according to investigator choice did show a survival benefit for cisplatin-based chemotherapy of 4.1% at 5 years; an interaction analysis showed no influence of radiotherapy on survival (10). The pragmatically designed Big Lung Trial in which radiotherapy and stage III patients were included did not find a survival difference for any of the chemotherapy arms. However, the confidence intervals of the Adjuvant Lung Cancer Project Italy, International Adjuvant Lung Trial, and Big Lung Trial and of the meta-analysis overlap and are consistent with a hazard ratio between 0.79 and 0.98, indicating a survival benefit (11). A summary of these four adjuvant CTRT trials, which included PORT for some patients and a variable proportion of stage III patients, are displayed in Table 1. The CALGB 9754 trial attempted to determine the value of PORT following resection and adjuvant chemotherapy but was closed due to poor accrual;
the results did not reveal a role for PORT (12). The preliminary results of two other trials that did not include stage III patients or PORT showed survival benefit with adjuvant platinum-based chemotherapy (13, 14). It could therefore be reasoned that there is no evidence that PORT in the adjuvant setting provides a survival benefit and should not be regarded as a standard after complete resection. However, this conclusion may be revised as systemic treatment becomes more effective in controlling distant metastases, with local regional recurrence then becoming the major survival determinant.

### Neoadjuvant: Chemotherapy before Surgery and Radiotherapy for Stages I to IIIA

The definitions of resectable, unresectable, minimal stage III, and bulky stage III are unclear in many reports and cause difficulties in grouping the data. Nevertheless, three fully published phase III trials investigated neoadjuvant chemotherapy, and PORT was given in some or all of the patients (15–17). The first two trials designed for stage IIIA primarily enrolled patients with N2 disease. In the Spanish study, PORT was planned to be given to all patients (15). Neoadjuvant chemotherapy, surgery, and PORT produced a significant improvement in survival over surgery and PORT, which resulted in the early stopping of the trial. The second study, also of 60 patients, was again stopped early, as there was a survival improvement with perioperative chemotherapy. Patients received three chemotherapy courses plus a further three if there was tumor regression; patients who were not completely resected could receive radiotherapy at the discretion of the treating physician. The influence of radiotherapy on outcomes was not examined (16). The third larger French study randomized 373 stage I to III patients to neoadjuvant chemotherapy or not, and two further chemotherapy courses were planned postoperatively for patients who responded to initial chemotherapy (17). In both arms, patients with pT3 and/or pN2 disease and incomplete resection were given PORT. There was a trend for increased survival in the chemotherapy arm, and a subgroup analysis suggested a survival benefit for N0 and N1 disease.

Other efforts attempted to determine the value of induction chemotherapy in stage IIIA followed by resection (when possible) versus radiotherapy without surgery but suffered generally from poor recruitment and emerging evidence at the time of the value of CTRT over radiotherapy alone (see Table 2; refs. 18–21). The largest trial had a somewhat unusual design, which randomized patients to neoadjuvant chemotherapy or no chemotherapy before surgery or curative intention radiotherapy; it reported a trend to longer survival with chemotherapy (20). The important European Organization for Research and Treatment of Cancer 08941 trial randomized initially inoperable N2 patients to surgery or radiotherapy after a response to initial chemotherapy; results are expected in 1 to 2 years. In a German Lung Cancer Cooperative Group trial, the addition of concurrent chemotherapy with twice-daily radiotherapy fractions following neoadjuvant chemotherapy before surgery (and PORT if incomplete resection) in stage III was of no benefit compared with a sequential approach of neoadjuvant chemotherapy alone then surgery and standard PORT fractionation (22).

The magnitude of the positive benefit from these trials is undefined, given the small patient numbers, heterogeneity of the population, the use of older regimens, and the variable use of radiotherapy. These studies suggest that neoadjuvant chemotherapy alone may be of value in resectable NSCLC but cannot be considered a standard approach when there is no clear contraindication to resection. Phase III trials (with no planned radiotherapy) are comparing neoadjuvant chemotherapy using newer platinum-based combinations with gemcitabine, taxanes, or vinorelbine followed by surgery to surgery alone in resectable NSCLC. Thus, the current focus is on neoadjuvant chemotherapy alone rather than combined CTRT followed by resection with or without adjuvant chemotherapy. There is then the question, which is better: neoadjuvant chemotherapy, adjuvant chemotherapy, or both approaches combined? Current trials will assist in answering some of these questions, although the lower rates of compliance with adjuvant compared with neoadjuvant chemotherapy could be a problem.

### Unresectable Stage III Disease: Chemotherapy and Radiotherapy Approaches

There are currently 13 possible T, N combinations within stage III, indicating the heterogeneity of the group and the need to define the study population more precisely in future studies. A meta-analysis of 1,780 patients from 11 trials showed a small survival advantage of 4% at 2 years, 2% at 5 years, with the addition of cisplatin-based chemotherapy to radiotherapy against radiotherapy alone (2). A subsequent trial confirmed the superior survival for patients receiving chemotherapy then standard radiotherapy versus radiotherapy alone. Hyperfractionated radiotherapy alone was not statistically

### Table 1. Adjuvant chemotherapy-PORT trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>% Stage IIIA patients</th>
<th>% Patients given radiotherapy per arm</th>
<th>Survival difference, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjuvant chemotherapy</td>
<td>No chemotherapy</td>
</tr>
<tr>
<td>ECOG (8)</td>
<td>59</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>ALPI (9)</td>
<td>28</td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>IALT (10)</td>
<td>39</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>BLT (11)</td>
<td>26</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

NOTE: The BLT trial included 3% of patients randomized in the neoadjuvant setting. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ALPI, Adjuvant Lung Cancer Project Italy; IALT, International Adjuvant Lung Trial; BLT, Big Lung Trial.

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superior to standard radiotherapy (23). More recently, the Eastern Cooperative Oncology Group 2597 study compared standard sequential CRTT against chemotherapy followed by hyperfractionated radiotherapy. Poor recruitment led to early closure; the survival was not significantly different between the two arms (24). In a British study using up to four courses of triplet chemotherapy then radiotherapy versus radiotherapy alone, there was a nonsignificant survival difference; however, quality of life was significantly better with chemotherapy (25). Higher doses of platinum have not improved survival (26). It is now generally recognized that chemotherapy given in addition to standard radiotherapy improves patient outcomes, and combined CRTT is a recommended approach in unresectable stage III NSCLC.

The converse situation of adding radiotherapy to a chemotherapy base was examined in a three-arm randomized trial that compared single-agent chemotherapy alone, standard radiotherapy alone, and chemotherapy plus radiotherapy. The 5-year survival rates of 1%, 3%, and 3%, respectively, were not significantly different, suggesting no survival benefit with immediate radiotherapy in unresectable tumors (27). Two other small randomized trials compared cisplatin chemotherapy followed by radiotherapy with cisplatin-based chemotherapy alone in unresectable disease (28, 29). A superior 3-year survival rate with sequential CRTT was reported in patients whose disease did not progress with initial chemotherapy (28). In the other study, patients whose disease responded to chemotherapy were randomized to further chemotherapy or radiotherapy; there was no survival difference between the two arms (29). There is perhaps then a provocative question as to whether immediate radiotherapy can be omitted in patients whose disease has responded to initial chemotherapy.

The two combined modality approaches used in treating locally advanced inoperable stage III disease include sequential administration of CRTT and concurrent CRTT. In two trials, no survival difference was found after induction chemotherapy by using radio-sensitizing chemotherapy doses concurrently with radiotherapy (30, 31). The European Organization for Research and Treatment of Cancer 08972 trial compared sequential CRTT against concurrent CRTT with daily (radio-sensitizing doses) of cisplatin but closed in March 2003 because of poor accrual; results are awaited. A meta-analysis of trials reported in the years 1987 to 1995 showed similar treatment effects when concurrent and sequential CRTT were considered separately (32). Since then, there have been two fully published trials (33, 34) and a number of abstracts of randomized phase II or III trials that have suggested some survival superiority (not all statistically significant) with the use of concurrent full-dose CRTT versus sequential CRTT, albeit with increased toxicity (see Table 3; refs. 33–38). The Japanese trial used different radiotherapy fractionation, split course in the concurrent arm but continuous in the sequential arm. Moreover, 59% of patients on the concurrent arm received one or two extra courses of chemotherapy after radiotherapy compared with 24.7% on the sequential arm (33). Similarly, in the Czech trial, 83% of patients in the concurrent group completed all four chemotherapy courses compared with 58% in the sequential group (34). The BROCAT German trial followed a more complicated design. After two cycles of induction chemotherapy, patients were randomized (if no progression) to radiotherapy alone or radiotherapy with concurrent single-agent chemotherapy; the survival was not statistically different between the two groups (see Table 3; ref. 38). The German trial and others indicate that induction chemotherapy followed by concurrent CRTT does not increase survival above that of sequential CRTT or concurrent CRTT alone (37–39). The recent Cochrane meta-analysis included 711 patients from three of the above trials meeting the selection criteria and confirmed the survival superiority of the concurrent approach (33–35, 40). There was a 14% reduction in the risk of death at 2 years ($P = 0.003$) but at the expense of more acute grade 3 to 4 esophagitis (33–35, 40). Other aspects of acute and late toxicity were not reported in all studies. Caution was advised in adopting concurrent CRTT as a standard because of uncertainties of the true magnitude of benefit in comparison with sequential CRTT and incomplete data on treatment-related morbidity (40). The question remains as to whether the survival in the sequential CRTT arms could have been improved by additional chemotherapy courses before thoracic radiotherapy was given (e.g., for a total of four rather than the two cycles commonly used).

### Conclusion

The major need is still to improve the systemic control of metastatic disease, which continues to be the prime cause of death in patients with early stage NSCLC. The predominance of the dated cisplatin/etoposide regimen with concurrent

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. patients</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd et al. (18)</td>
<td>31</td>
<td>CT-S: 18, RT: 16</td>
</tr>
<tr>
<td>Stephens et al. (21)</td>
<td>42</td>
<td>CT-S: 14, RT: 11</td>
</tr>
<tr>
<td>Johnstone et al. (19)</td>
<td>75</td>
<td>CT-S-CT: 19.4, CT-RT-CT: 17.4</td>
</tr>
<tr>
<td>Mattson et al. (20)</td>
<td>274 (stages IIIA, B)</td>
<td>CT-S-CT: 15, S or RT: 13</td>
</tr>
</tbody>
</table>

Abbreviations: CT, chemotherapy; S, surgery; RT, radiotherapy.
radiotherapy has perhaps focused undue attention on incorporating this regimen into recent trials; exploitation of new drug regimens followed by novel thoracic radiotherapy approaches would allow greater clinical trial design freedom and perhaps result in greater metastatic and local control. Furthermore, only a selected proportion of patients have been included in the recent studies of concurrent CTRT, including those with better performance status, better lung function, least tumor volume, and least comorbidity. There remains a need to develop the sequencing of combined modality treatment for the broader patient population.

Open Discussion

**Dr. Thomas Lynch**: One of the points is that these concurrent regimens handcuff our ability to use certain systemic agents. Dr. Vokes was successful using gemcitabine with radiation, but few others have been.

**Dr. Everett Vokes**: Regarding gemcitabine, I’m not sure that we have completely characterized its safety and efficacy in stage III disease. But 9431 was a Group effort and not a single institutional experience. That strengthens its findings. However, if you look at those data [Vokes et al., J Clin Oncol 2003;21:2004–10] may have been so successful is that the Schaake-Koning study [N Engl J Med 1992;326:524–30] showed; that low-dose daily platinum actually improved survival based solely on improving local control with no impact on distant metastases. So, if you can incorporate full-dose chemotherapy concurrently, then that might be a goal.

**Dr. Lynch**: That is one of the hopes of Dr. Vokes’ work, the fact that you can give pemetrexed and carboplatin at full doses would certainly be aligned with what Dr. Gandara is suggesting. In fact, one of the reasons that the SWOG 9504 study [J Clin Oncol. 2003;21:2004–10] may have been so successful is that cisplatin and etoposide were given at full systemic dosing.

**Dr. Vokes**: That argument is why I am surprised about the studies giving induction chemotherapy before concomitant chemoradiotherapy not being more positive. I always hypothesized that giving full-dose chemotherapy early and the radiation a little later for a solid tumor where failure occurs predominantly systemic would be beneficial. It is counterintuitive, but the data are coming out the other way.

**Dr. Bruce Johnson**: I think it is because more patients end up getting both modalities when you do the radiation earlier, so it is the drop-off phenomenon rather than early versus late.

**Dr. Lynch**: We really seem to have reached a plateau in stage III disease, as Chandra Belani says we have in stage IV disease. What are the numbers that we would want to see in order to be excited about doing a large phase III trial? Let’s say Dr. Vokes goes ahead and does a pilot phase II with pemetrexed and platinum. Can people throw out some numbers for the median survival they would want to see before designing the next Intergroup study, based on what we know so far?

---

**Table 3. Completed trials of chemoradiotherapy sequencing in unresectable stages IIIA and IIIB**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. patients</th>
<th>CT cycles, RT dose</th>
<th>Median survival (mos)</th>
<th>Actuarial survival (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequential</td>
<td>Concurrent</td>
<td></td>
</tr>
<tr>
<td>Furuse et al. (33)</td>
<td>320</td>
<td>CT × 2, 56 Gy, vCT</td>
<td>13.3</td>
<td>16.5</td>
<td>9 (5 y) 16 (5 y) 0.04</td>
</tr>
<tr>
<td>Zatloukal et al. (34)</td>
<td>102</td>
<td>CT × 4, 60 Gy</td>
<td>12.9</td>
<td>16.6</td>
<td>9 (3 y) 19 (3 y) 0.02</td>
</tr>
<tr>
<td>Curran et al. (35)</td>
<td>402</td>
<td>CT × 2, 60 Gy</td>
<td>14.6</td>
<td>17.0</td>
<td>12 (4 y) 21 (4 y) 0.046</td>
</tr>
<tr>
<td>Fournel et al. (36)</td>
<td>212</td>
<td>CT × 2, 46 Gy</td>
<td>13.8</td>
<td>15.0</td>
<td>23 (2 y) 35 (2 y) NS</td>
</tr>
<tr>
<td>Bonomi et al. (37)</td>
<td>184</td>
<td>CT × 2, 83 Gy</td>
<td>13.1</td>
<td>16.1</td>
<td>28 (2 y) 31 (2 y) NS</td>
</tr>
<tr>
<td>Huber et al. (38)</td>
<td>303</td>
<td>CT × 2/60 Gy</td>
<td>14.1</td>
<td>18.7</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE: For the three-arm phase III trial of Curran, the sequential CT-RT versus concurrent CT/standard RT fractionation are given (34).

For the three-arm phase II trial of Bonomi, the sequential CT-RT versus concurrent CT/RT then consolidation CT arm are given; 2-year survival rates are estimated (36). Abbreviations: vCT, variable number of CT courses post-RT; CT, chemotherapy; RT, radiotherapy; NS, not significant.

This is exactly what was shown in the LAMP study as well. With induction chemotherapy first, concurrent afterwards, a lot of the patients drop off along the way because of progressive disease, so they don’t complete the therapy. So, the fact that fewer people completed the radiation, I think, points to the fact that concurrent is better in addressing both compartments, local and systemic. I realize you can interpret it different ways, but that is my interpretation of that point.

**Prof. Nick Thatcher**: It is a discussion point, really. Our patients are dying of systemic disease, so it seems to me that we need more focus on delivery of the best chemotherapy that we can, and I have a feeling that two courses simply aren’t enough.

**Dr. Gandara**: A lot of the concurrent therapies give ineffective systemic doses together with radiation and that’s what we have completely characterized its safety and efficacy in stage III disease. But 9431 was a Group effort and not a single institutional experience. That strengthens its findings. However, if you look at those data [Vokes et al., J Clin Oncol 2003;21:2004–10] may have been so successful is that the Schaake-Koning study [N Engl J Med 1992;326:524–30] showed; that low-dose daily platinum actually improved survival based solely on improving local control with no impact on distant metastases. So, if you can incorporate full-dose chemotherapy concurrently, then that might be a goal.

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Dr. Glenwood Goss: We have seen lots of phase II studies of concurrent chemotherapy and hyperfractionation that have median durations of survival between 14 and 20 months. The SWOG 9504 data are the best, and that is 26 months. If we do a phase III study, we need control arms that are 20 months or so, it would tell us a great deal.

Dr. Walter Curran: The ironic part is that NCI did not approve a study of the SWOG 9504 regimen versus a standard regimen in phase II. So our opinion is of interest, but may not allow such a study to go forward.

Dr. Gandara: One saving grace is in the current Intergroup 0023, which is concurrent chemoradiotherapy followed by consolidation docetaxel randomized to gefitinib or not. The control arm will basically reproduce the SWOG regimen in 400 patients. Even if gefitinib turns out to improve survival, if the control arm is still 20 months or so, it would tell us a great deal.

Dr. Vokes: But you would then have a three-element regimen as standard, of which only two elements would have been proven. You still wouldn't know about the need for consolidation chemotherapy.

Dr. Johnson: We're talking about hypothetical information. We will get more data, and if it is important to sort out the docetaxel question, we will then design a study to answer that.

Prof. Thatcher: I'd like to understand what happens in the U.S. and Canada with patients who are not eligible for your concurrent chemoradiotherapy approaches. Is it possible to think about a trial using sequential chemotherapy and radiotherapy in such a group of patients?

Dr. Curran: Dr. Gandara and others in SWOG have done reduced intensity concurrent regimens in such patients and seen good progress [J Clin Oncol 1998;16:3078–81].

Dr. Gandara: Yes, with carboplatin, etoposide, and radiation at 61 Gy. No toxic deaths.

References


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