Final Results of Phase III Trial in Regionally Advanced Unresectable Non-Small Cell Lung Cancer*

Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group

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Study objectives: The purpose of this phase III clinical trial was to test whether chemotherapy followed by radiation therapy resulted in superior survival to either hyperfractionated radiation or standard radiation in surgically unresectable non-small cell lung cancer.

Design: Patients were prospectively randomized to 2 months of cisplatin, vinblastine chemotherapy followed by 60 Gy of radiation at 2.0 Gy per fraction or 1.2 Gy per fraction radiation delivered twice daily to a total dose of 69.6 Gy, or 2.0 Gy per fraction of radiation once daily to 60 Gy. Patients were enrolled from January 1989 through January 1992, and followed for a potential minimum period of 5 years.

Setting: This trial was an intergroup National Cancer Institute–funded trial within the Radiation Therapy Oncology Group, the Eastern Cooperative Oncology Group, and the Southwest Oncology Group.

Patients: Patients with surgically unresectable non-small cell lung cancer, clinical stage II, IIIA, and IIIB, were required to have a Karnofsky Performance Status of ≥ 70 and a weight loss of < 5% for 3 months before study entry. Four hundred ninety patients were registered on trial, of which 458 patients were eligible.

Conclusion: Overall survival was statistically superior for the patients receiving chemotherapy and radiation vs the other two arms of the study. The twice-daily radiation therapy arm, although better, was not statistically superior in survival for those patients receiving standard radiation. Median survival for standard radiation was 11.4 months; for chemotherapy and irradiation, 13.2 months; and for hyperfractionated irradiation, 12 months. The respective 5-year survivals were 5% for standard radiation therapy, 8% for chemotherapy followed by radiation therapy, and 6% for hyperfractionated irradiation.

Key words: chemotherapy; hyperfractionated radiation; lung cancer; phase III trial; radiation

Abbreviations: CALGB = Cancer and Leukemia Group B 8433; KPS = Karnofsky Performance Status; RTOG = Radiation Therapy Oncology Group

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Regionally advanced non-small cell lung cancer represents the most common presentation of the most common cause of cancer death in the United States. Survival for regionally advanced non-small cell lung cancer is extremely poor. Controversy exists as to whether nonsurgical treatment in these patients is capable of substantially altering the course of the disease. Local regional radiation therapy has represented the traditional approach in these patients, inasmuch as it represents, at a minimum, a useful palliative tool and has resulted in occasional long-term survival. In attempts to improve the survival in these patients, many investigators have added cytotoxic chemotherapy to external beam irradiation. Several phase III trials have been equivalent, but more recently, several trials have been positive in favor of combined therapy. This trial was designed to confirm the results of Cancer and Leukemia Group B 8433 (CALGB), which used induction chemotherapy followed by irradiation.

This trial was also designed to test hyperfractionated irradiation. Hyperfractionated irradiation is treatment that delivers radiation more than once daily at total daily doses similar to that of standard radiation and with an increase in overall total dose. A previous phase II/III Radiation Therapy Oncology Group (RTOG) trial suggested that hyperfractionated irradiation represented a therapeutic advantage to standard irradiation. An important component of this trial was preselection of patients for good performance. It has been recognized that patients with excessive weight loss and poor Karnofsky Performance Status (KPS) do poorly with nonsurgical therapy. For this reason, this trial, as well as many others, included only patients with minimal weight loss and relatively good performance status.

**Materials and Methods**

Methods have been previously described. Eligibility included patients who were surgically inoperable with American Joint Committee on Cancer stage II, IIIA, or IIIB non-small cell lung cancer. Patients were required to have a KPS ≥ 70 and a weight loss of < 5% for 3 months before study entry, to be > 18 years of age, and to have no metastatic disease. Surgical staging was not required. Patients with pleural effusions were excluded from study participation. Pretreatment evaluation required a complete history and physical examination, chest radiograph with thoracic and upper abdominal CT, and laboratory studies (including a CBC count, platelet count, measurements of calcium and bilirubin concentrations, urine analysis, and liver function studies). Pulmonary function tests consisting of vital capacity, FEV1, and carbon monoxide diffusing capacity of the lung were required of the patients. Patients who had received prior chemotherapy or irradiation were excluded from study participation, and patients who had undergone curative surgical procedures were also excluded. Patients signed a study-specific consent form that had been approved by the institutional review board and all participating institutions.

Statistical variables included histologic cell type, KPS, and clinical stage. The sample size was selected to detect a 49% improvement in median survival in the experimental arm, with a p < 0.05 and a power of ≥ 80%. Theoretically, this study would observe an improvement from a standard treatment arm median survival of 8.7 months to experimental treatment arm median survival of 13 months. We determined that 161 patients would need to be registered in each treatment arm to ensure a statistical validity of our observation. Our total registered sample size would be 483 patients for the lifetime of the study. The Study Monitoring Committee evaluated the study midway through accrual to ensure that no one treatment arm was statistically superior and that accrual could continue as planned.

The standard radiation therapy arm (arm 1) and the induction chemotherapy arm (arm 2) had similarly delivered irradiation. Irradiation was delivered at 2 Gy per fraction, 5 days a week, to a total dose of 60 Gy. There were no corrections for lung inhomogeneity. Regional lymphatics, including the supraclavicular lymph nodes when the primary tumor was in the upper lobes or mainstem bronchi, were included in the initial radiation volume. The field included a 2-cm margin on the ipsilateral hilar lymph nodes and a 1-cm margin on the contralateral hilar lymph nodes. The subcarinal lymph nodes were included to 3 cm below the carina. The regional lymphatics were treated to a total dose of 50 Gy at 2 Gy per fraction followed by a boost dose to the primary neoplasm and all lymph nodes > 2.5 cm in diameter visualized on CT scan before chemotherapy. The boost dose included a 2-cm margin around the radiographically visible tumor, and the dose was continued to 60 Gy. The spinal cord dose was limited to 45 Gy in treatment arms 1 and 2 of the study and to 50 Gy in the hyperfractionated arm (treatment arm 3). A posterior spinal cord block was not allowed in any arms of this study. The hyperfractionated radiation therapy arm (arm 3) consisted of 1.2 Gy per fraction delivered twice daily (consecutive days, 5 days per week until total dose achieved) to a total dose of 69.6 Gy. The study required treatments to be 4 to 6 h apart, with field reduction occurring at 50.4 Gy. Field sizes and target volumes in arm 3 were similar to those in arms 1 and 2. The dosimetry staff and one investigator (W.T.S.) at RTOG headquarters retrospectively reviewed all field arrangements, target volumes, and dosimetry.

Treatment arm 2, which consisted of cisplatin and vinblastine before irradiation, required that irradiation began on day 50. The cisplatin (100 mg/m2) was administered IV for a 30- to 60-min period on days 1 and 29. Adequate hydration was begun 24 h before the use of cisplatin. Vinblastine (5 mg/m2) was administered IV bolus weekly for 5 consecutive weeks beginning on day 1 with cisplatin. Dose modifications were incorporated into the trial and were based on the granulocyte and platelet counts. One of us (S.T.) retrospectively reviewed all flow sheets to evaluate chemotherapy. Central pathology review was not required in this trial, inasmuch as previously conducted trials established good concordance between institutional and central reviews.

After completion of treatment, patients were evaluated every 2 months for up to 6 months, then every 3 months for 2 years, then every 6 months. Follow-up evaluation included a plain radiograph of the chest, liver function studies, and CBC counts. More sophisticated work-up was performed only if indicated. Sites and times of recurrence were to be documented. Survival and time to incidence of toxic effects were measured from the date of registration on study. In the computation of the time-adjusted incidence of toxicity, a bias associated with censoring patients who died without morbidity may occur; to correct for this bias, conditional probabilities were used. Survival estimates were...
computed by the product-limit method. The time to treatment morbidity and survival were plotted as a step function. Testing for difference in survival distribution was performed using the log-rank status and the generalized Wilcoxon test. The latter test is more sensitive to an early difference in the survival distributions. All statistical tests were two-sided.

The study opened on January 20, 1989, and closed on January 25, 1992, with a total accrual of 490 patients. RTOG institutions placed 348 patients on trial; Eastern Cooperative Oncology Group institutions, 115 patients; and Southwest Oncology Group institutions, 27 patients. All patients were followed for a minimum of 5 years or until death. The potential minimum follow-up was 5 years. Thirty-two of the 490 patients entered in the trial were either ineligible or had no analyzable data, which resulted in a study population of 458 patients (Table 1). Table 2 shows the pretreatment characteristics of the patients. Approximately 45% of the patients in all treatment arms had stage IIIA disease and approximately 50% had stage IIIB disease. Twenty-three patients had T3N0 tumors; 9 of these patients were treated by standard radiation therapy, 9 by chemotherapy and irradiation, and 5 by hyperfractionated radiation therapy. As noted in Table 2, tumor stage and histology were uniformly divided in all treatment arms. Two thirds of the patients had a KPS of 90 to 100.

Results

Compliance to protocol was acceptable. Approximately 80% of patients received treatment per protocol with minor variation of protocol delivery. Major acceptable variations in treatment were seen in only 5% of patients registered on treatment. One hundred twenty-two of 151 patients had chemotherapy delivered by protocol. Table 3 outlines the delivery of systemic therapy. Toxicity was acceptable. There were six grade 4 or worse acute radiotherapy-related toxic events: four on the hyperfractionated radiation arm, one on the standard radiation therapy arm, and one on the chemoradiotherapy plus radiation therapy arm. Two of the four toxic effects of hyperfractionated radiation therapy were secondary to esophagitis. Two patients on trial died of pulmonary toxicity secondary to irradiation, one patient on the chemoradiotherapy plus radiation therapy and one on the hyperfractionated radiation arm. Two chemotherapy-related deaths were reported. Both were secondary to infection before the commencement of irradiation. Table 4 represents the toxicity.

Table 5 and Figure 1 reflects the survival for all patients entered on trial, with a minimum potential follow-up of 5 years. The median survival for those

### Table 1—Case Status*

<table>
<thead>
<tr>
<th>Status</th>
<th>Standard RT</th>
<th>CT + RT</th>
<th>HFX RT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomly accrued, No.</td>
<td>163</td>
<td>164</td>
<td>163</td>
<td>490</td>
</tr>
<tr>
<td>Patients ineligible—no protocol therapy, No.</td>
<td>10</td>
<td>12</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Eligible patients, No.</td>
<td>153</td>
<td>152</td>
<td>157</td>
<td>462</td>
</tr>
<tr>
<td>Patients with no registration form, No.</td>
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<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Patients properly entered and eligible, No.</td>
<td>152</td>
<td>152</td>
<td>154</td>
<td>458</td>
</tr>
</tbody>
</table>

*RT = radiation therapy; CT = chemotherapy; HFX = hyperfractionated

### Table 2—Patient Characteristics by Assigned Treatment*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard RT (n = 152)</th>
<th>CT + RT (n = 152)</th>
<th>HFX RT (n = 154)</th>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>105 (69)</td>
<td>109 (72)</td>
<td>108 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>47 (31)</td>
<td>43 (28)</td>
<td>46 (30)</td>
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<tr>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>90–100</td>
<td>100 (66)</td>
<td>106 (70)</td>
<td>106 (69)</td>
</tr>
<tr>
<td>70–80</td>
<td>52 (34)</td>
<td>46 (30)</td>
<td>48 (31)</td>
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<tr>
<td>Histologic diagnosis</td>
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<td></td>
<td></td>
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<tr>
<td>Squamous</td>
<td>68 (45)</td>
<td>66 (43)</td>
<td>68 (44)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>50 (33)</td>
<td>57 (38)</td>
<td>48 (31)</td>
</tr>
<tr>
<td>Large cell</td>
<td>13 (8)</td>
<td>17 (11)</td>
<td>22 (14)</td>
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<tr>
<td>Squamous/adenocarcinoma</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>1 (1)</td>
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<td>Carcinoma not otherwise specified</td>
<td>9 (6)</td>
<td>3 (2)</td>
<td>8 (5)</td>
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<td>Other</td>
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<td>6 (4)</td>
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<tr>
<td>T stage</td>
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<tr>
<td>T1</td>
<td>12 (8)</td>
<td>17 (11)</td>
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<td>T2</td>
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<td>I</td>
<td>9 (6)</td>
<td>10 (6)</td>
<td>7 (4)</td>
</tr>
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<td>IIIA</td>
<td>67 (44)</td>
<td>68 (45)</td>
<td>71 (46)</td>
</tr>
<tr>
<td>IIIB</td>
<td>76 (50)</td>
<td>74 (48)</td>
<td>76 (50)</td>
</tr>
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</table>

No. (%) of patients by treatment.
See footnote for Table 1 for abbreviations.

Table 3—Delivery of Systemic Therapy*

<table>
<thead>
<tr>
<th>Vinblastine Courses</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>1 Course</td>
<td>0</td>
</tr>
<tr>
<td>2 Courses</td>
<td>0</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>1</td>
</tr>
</tbody>
</table>

*Number of patients. Flow sheet not available for eight patients.
receiving standard irradiation was 11.4 months, and the 5-year survival was 5%. The median survival for those receiving chemotherapy plus irradiation was 13.2 months, with a 5-year survival of 8%; those patients who received hyperfractionated irradiation experienced a median survival of 12 months with a 5-year survival of 6%. The log-ranked statistical comparison indicated chemotherapy plus irradiation resulted in a superior survival equal to \( p < 0.04 \).

Several patients were lost to follow-up resulting in some discrepancies in survival denominator. Subset analysis was performed to detect a sub-group of patients which may benefit more substantially from a particular arm of treatment. Analysis was performed comparing histology and age to treatment, which failed to reveal any known predictive factors other than age, which was statistically significant for those patients receiving cytotoxic chemotherapy. For patients < 60 years of age, median survival for radiation therapy alone was 11.7 months; for hyperfractionated irradiation, 11.5 months; and for standard irradiation with chemotherapy, 15.4 months. On the other hand, for patients > 70 years of age, the survival was best with standard radiation therapy alone, with a median survival of 13.1 months. The median survival for chemotherapy followed by irradiation was 10.9 months. All toxic deaths secondary to chemotherapy were in patients > 70 years. In the entire study, 66 patients were > 70 years, 214 between 60 and 70 years, and 172 < 60 years of age, well balanced between treatment arms.

Chemotherapy and irradiation was most effective for nonsquamous cell types, with a median survival for standard irradiation of 11.4 months and for radiation plus chemotherapy, 15.6 months. Although not statistically significant, those patients with squamous cell carcinoma treated with hyperfractionated irradiation exhibited a 9% 5-year survival compared with 2% in each of the other treatment arms.

**Discussion**

The purpose of this trial was to test the hypothesis that either induction chemotherapy followed by irradiation or hyperfractionated irradiation would provide superior survival to standard irradiation in regionally advanced non-small cell lung cancer. This trial represents the largest trial in North America comparing standard irradiation to chemotherapy followed by irradiation in regionally advanced non-small cell lung cancer, and the only phase III trial comparing hyperfractionated irradiation to standard irradiation in regionally advanced non-small cell lung cancer. Our trial suggests that aggressively applied, nonsurgical treatment can statistically improve the survival and alter the natural history of this disease. In our trial, the patients who exhibited the best survival were those patients treated with induction chemotherapy followed by irradiation. This confirms a previous study conducted by the CALGB in the United States.8

Several studies have been conducted worldwide comparing irradiation therapy alone with irradiation therapy and chemotherapy.3–11 Although many of these trials have been equivalent,5,6,9–11 several of the more recently conducted trials using cisplatin-

<table>
<thead>
<tr>
<th>Table 4—Acute and Late Toxicity*</th>
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</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td>Acute &gt; grade III radiation</td>
</tr>
<tr>
<td>Acute &gt; grade III chemotherapy</td>
</tr>
<tr>
<td>Late &gt; grade III radiation†</td>
</tr>
</tbody>
</table>

*No. of patients. See Table 1 footnote for abbreviations.
†All grade V toxicity (death) occurred in patients > 60 years of age.
‡Late toxicity is ≥ 90 days after treatment.

<table>
<thead>
<tr>
<th>Table 5—Overall Survival by Treatment Arm for all Patients*</th>
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</thead>
<tbody>
<tr>
<td><strong>Years</strong></td>
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<tr>
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</tr>
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</tr>
<tr>
<td>1</td>
</tr>
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<td>2</td>
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<td>3</td>
</tr>
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<td>4</td>
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<td>5</td>
</tr>
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<td>Dead/Total</td>
</tr>
<tr>
<td>p value</td>
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</tbody>
</table>

*See footnote for Table 1 for abbreviations.
†Three patients in the RT/CT group and five patients in the HFX group were lost to follow-up on study information.
based chemotherapy have been positive in favor of combined therapy.\textsuperscript{3,4,8,12} One published meta-analysis also suggests that cisplatin-based chemotherapy added to irradiation provides a statistical improvement in survival.\textsuperscript{21} The survival benefit noted in our trial is substantially less impressive than that observed by the CALGB. The survival benefit in our trial is more in line with previously conducted trials in France\textsuperscript{3} and in Great Britain.\textsuperscript{9} The French trial did reach statistical significance, whereas the recent trial conducted by the Medical Research Council did not reach statistical significance.

Because the benefits of combined therapy are relatively small, we performed a subset analysis to see whether we could discover a subgroup most likely to benefit from aggressive treatment. Our analysis suggests that age represented a factor that may predict a better survival to cytotoxic chemotherapy and irradiation. Interestingly, those patients >70 years of age seemed to benefit from the least aggressive treatment arm. Only 66 patients >70 years old were registered in the study. This makes sound conclusions regarding this observation difficult. Underrepresentation of elderly on clinical trials is not unique to this study.\textsuperscript{22} Interestingly, the CALGB trial, which suggested a more dramatic benefit to combined therapy, had a greater proportion of patients <60 years of age (45\%) and fewer patients with squamous cell cancer (36\%) in the combined arm than our trial.\textsuperscript{23}

One should note that all patients in this protocol were selected for protocol participation. All patients treated in this study had high performance status and minimal weight loss before enrollment. Extrapolation of this aggressive form of therapy to other clinical subgroups may not be appropriate. The RTOG has also attempted to analyze sites of failure to define the reason for benefit to combined therapy.\textsuperscript{24} The results of the sites of failure analysis are conflicting and probably relate to the difficulty of performing accurate sites of failure analysis in large intergroup trials containing patients with lung cancer.

This study failed to confirm a benefit of hyperfrac-
tionated irradiation. Although the median survival of those patients treated with multiple daily fractions was intermediate to those receiving combined therapy and standard irradiation, this failed to reach statistical significance. Interestingly, in squamous cell disease, the 5-year survival was 9% vs 2% in the other two treatment arms. The Medical Research Council of Great Britain has recently completed an accelerated radiotherapy trial in regionally advanced non-small cell lung cancer. In this trial, patients were randomized to receive either standard irradiation or irradiation delivered 150 cGy, three times per day for 12 consecutive days. This aggressive approach provided a statistical improvement in survival to those patients on the experimental arm. Interestingly, approximately 80% of patients treated in the Great Britain trial had squamous cell cancer. It may be that aggressively applied irradiation would be most beneficial in squamous cell disease, whereas chemotherapy and irradiation may provide more benefit in nonsquamous cell cancers, an observation that will need confirmation in other clinical trials.

This large phase III trial does confirm our ability to alter the natural history of regionally advanced non-small cell lung cancer with aggressively applied nonsurgical therapy. Although the degree of improvement is relatively small, the frequency of this disease reflects a potential benefit to large numbers of patients. Around the world, groups are enrolling patients in clinical trials that are attempting to improve on these results. Hopefully, refinements in these observations will allow more selective and more sophisticated application of aggressive nonsurgical therapies in patients with regionally advanced non-small cell lung cancer.

**REFERENCES**


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