Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non–Small-Cell Lung Cancer: KCSG-LU05-04


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ABSTRACT

Purpose
To determine the efficacy of consolidation chemotherapy (CC) with docetaxel and cisplatin (DP) after concurrent chemoradiotherapy (CCRT) with the same agents in locally advanced non–small-cell lung cancer (LA-NSCLC).

Patient and Methods
Patients were randomly assigned to either CCRT alone (observation arm) or CCRT followed by CC (consolidation arm). CCRT with docetaxel (20 mg/m²) and cisplatin (20 mg/m²) was administered every week for 6 weeks with a total dose of 66 Gy of thoracic radiotherapy in 33 fractions. In the consolidation arm, patients were further treated with three cycles of DP (35 mg/m² each on days 1 and 8, every 3 weeks). The primary end point was 40% improvement in progression-free survival (PFS) compared with observation.

Results
From October 2005 to April 2011, 437 patients were randomly assigned. Seventeen patients did not start CCRT as a result of consent withdrawal or ineligibility reasons after random assignment, leaving 420 patients for this analysis (n = 211 for observation; n = 209 for consolidation). Patient characteristics were similar in both arms. In the consolidation arm, 143 patients (68%) received CC, of whom 88 (62%) completed three planned cycles. The median PFS was 8.1 months in the observation arm and 9.1 months in the consolidation arm (hazard ratio, 0.91; 95% CI, 0.73 to 1.12; P = .36). Median overall survival times were 20.6 and 21.8 months in the observation and consolidation arms, respectively (HR, 0.91; 95% CI, 0.72 to 1.25; P = .44).

Conclusion
CC with DP after CCRT with weekly DP in LA-NSCLC failed to further prolong PFS. CCRT alone should remain the standard of care.

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INTRODUCTION

The incidence of lung cancer is still increasing in most countries, and it remains the leading cause of cancer death.1,2 Non–small-cell lung cancer (NSCLC) accounts for approximately 80% to 85% of lung cancer. Most patients with NSCLC are detected with locally advanced or metastatic disease and have poor survival.3

Inoperable locally advanced NSCLC (LA-NSCLC) has shown an approximately 5% 5-year survival rate with radiation therapy (RT) alone.4 For the treatment of LA-NSCLC, multidisciplinary therapy has resulted in survival improvements. In the 1980s, induction chemotherapy was investigated for LA-NSCLC, and several randomized phase III studies of induction chemotherapy and subsequent RT have reported significant increases in survival.5-7 In the 1990s, a new approach with the concurrent administration of chemotherapy and RT was introduced and demonstrated further improvements in survival compared with RT alone.8-10 Subsequent randomized phase III trials have confirmed the superiority of concurrent chemoradiotherapy (CCRT) compared with sequential chemoradiotherapy.11,12 Since then, the standard of care for LA-NSCLC has been CCRT.
Despite this progress with a combined-modality approach, the prognosis of LA-NSCLC remains poor, with a median survival time of 15 to 18 months. In 2003, the Southwest Oncology Group 9504 trial, a phase II trial for consolidation chemotherapy (CC) with docetaxel after CCRT with etoposide and cisplatin (EP), reported promising results with a median progression-free survival (PFS) of 16 months and a median survival of 26 months.

In a previous phase II study of CCRT with CC and oral etoposide and cisplatin for LA-NSCLC, we reported promising response rates and survival results. We also conducted a phase I study of weekly docetaxel and cisplatin (DP) concurrent with thoracic RT in stage III NSCLC and confirmed the feasibility of this regimen with acceptable toxicities. On the basis of these studies, this phase III randomized trial was designed to evaluate whether CC with these same third-generation chemotherapeutic agents after CCRT with weekly DP provides survival benefit for patients with inoperable stage III NSCLC.

**Patients and Methods**

Patients with histologically documented NSCLC with inoperable stage IIIA or IIIB disease, which was proven by computed tomography (CT), magnetic resonance imaging, and/or positron emission tomography (PET), were eligible. N2 or N3 disease must have been confirmed by pathology or PET. Patients were age 18 years or older and had an Eastern Cooperative Oncology Group performance status of 0 to 1 at baseline.

Eligible patients also met the following criteria: measurable disease based on RECIST; no prior chemotherapy, RT to the chest, immunotherapy, or biologic therapy; forced expiratory volume in 1 second ≥ 0.8 L by spirometry; and adequate bone marrow, renal, and hepatic function. Female patients were also excluded if they were pregnant or lactating, had not taken a pregnancy test within 14 days before the first administration, or had childbearing potential and were not willing to use adequate contraception.

All patients provided written informed consent. The study was approved by the institutional review board of every participating institution and was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice.

**Study Design and Treatment**

This was an international, multicenter, open, randomized, phase III study to evaluate the effects of CC of DP after CCRT in patients with inoperable LA-NSCLC. Random assignment was performed through a computerized online system. The stratification factors were participating center and performance status.

Eligible patients received docetaxel 20 mg/m² intravenously and cisplatin 20 mg/m² intravenously on days 1, 8, 15, 22, and 29. All patients received thoracic RT 5 days per week in once-daily fractions and at 2.0 Gy per fraction. The total dose was 66 Gy in 33 fractions. The initial 46 Gy or RT over 23 fractions covered the clinical target volume plus the margin, and the later 20 Gy or 10 fractions covered the gross tumor volume plus the margin. CC was conducted between 4 and 8 weeks after the completion of CCRT in patients with no local progression or distant metastases and the margin. CC was obtained before the first administration, or had childbearing potential and were not willing to use adequate contraception.

All patients provided written informed consent. The study was approved by the institutional review board of every participating institution and was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice.

**RESULTS**

Between October 2005 and April 2011, 459 patients from 31 centers in Korea, China, and Taiwan were screened for the study. Among them, 437 patients were eligible and were allocated to the observation arm (n = 219) or consolidation arm (n = 218). Eight patients from the observation arm and nine patients from the consolidation arm did not start CCRT because of consent withdrawal or ineligibility reasons, leaving 420 patients in the study (n = 211 for observation; n = 209 for consolidation). These 420 patients were included in the final analysis cohort (Fig 1). Patient characteristics are listed in Table 1. Approximately half of the patients had adenocarcinoma histology, and approximately 80% had stage IIIB disease. Demographic baseline characteristics were well balanced between the two groups.

**Statistical Analysis**

The primary objective was to show that the consolidation arm would increase the median PFS by 40% from the PFS of 12 months reported from observation by Park et al. PFS was defined as the time from random assignment to the first documentation of disease progression or death, whichever came first. With a total of 434 patients (n = 217 per arm), we had 90% power by the log-rank test with a two-sided α = .05. The sample size calculation was based on the following assumptions: 10% of attrition, 18 months of additional follow-up, and an annual accrual of 72 patients. A preplanned interim analysis after 50% of enrollment demonstrated no safety issues and was previously reported in 2009.

The secondary end points included a comparison of overall survival (OS), overall response rate, patterns of failure, and toxicities between the two arms. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 3.0. Descriptive statistics used medians or proportions with their appropriate measures of distribution. The Kaplan-Meier method was used to estimate the distribution of PFS and OS, and the distribution of each end point was compared between the two treatment arms using the log-rank test. Univariable and multivariable regression analyses were conducted on PFS using the Cox regression method. All P values are two-sided. We considered P < .05 to be significant. The exploratory end point was to investigate the correlation of tissue expression of ERCC1 and class III β-tubulin with the clinical outcome.

**Exploratory Biomarker Study**

Formalin-fixed, paraffin-embedded, 4 μm-thick tissue sections were labeled with mouse monoclonal anti-ERCC1 antibody (8F1; Gene Tex, Irvine, CA) and anti–β3-tubulin antibody (TU-20; Santa Cruz Biotechnology, Santa Cruz, CA). Immunostaining was performed using a Bond-max autoimmunostainer with Bond Polymer refine detection, DS9800 (Leica Biosystems, Melbourne, Australia). Immunohistochemical evaluation was performed by a pathologist without knowledge of the clinical data. Tumor staining intensity was graded on a scale of 0 to 3 using adjacent nonmalignant cells as a reference (intensity of 2). One hundred to 1,500 positive or negative tumor cells per specimen were counted manually. The percentage of positive tumor cells was counted for each specimen. This proportional percentage was multiplied by the staining intensity to obtain a final semiquantitative H score (Appendix Fig A1, online only).

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Consolidation Arm (n = 218)</th>
<th>Observation Arm (n = 211)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>66 (21-83)</td>
<td>67 (21-83)</td>
<td>.66</td>
</tr>
<tr>
<td>Sex, male</td>
<td>139 (64%)</td>
<td>137 (65%)</td>
<td>.83</td>
</tr>
<tr>
<td>Performance status, 0-1</td>
<td>203 (93%)</td>
<td>200 (94%)</td>
<td>.58</td>
</tr>
<tr>
<td>Prior thoracic RT, no</td>
<td>412 (95%)</td>
<td>411 (95%)</td>
<td>.76</td>
</tr>
<tr>
<td>Prior thoracic RT, yes</td>
<td>7 (2%)</td>
<td>6 (3%)</td>
<td></td>
</tr>
<tr>
<td>Prior concomitant therapy</td>
<td>10 (5%)</td>
<td>10 (5%)</td>
<td>.47</td>
</tr>
<tr>
<td>Prior concomitant therapy</td>
<td>21 (10%)</td>
<td>14 (7%)</td>
<td>.02</td>
</tr>
<tr>
<td>Prior concomitant therapy</td>
<td>11 (5%)</td>
<td>7 (3%)</td>
<td>.04</td>
</tr>
</tbody>
</table>
Treatment Exposure During Consolidation

Of the 209 patients randomly assigned to the consolidation arm, 42.1% received all of the three planned cycles, and 54.1% finished at least two cycles (Table 2). Sixty-six patients (31.6%) did not receive any CC. The reasons for not receiving CC included early death (n = 11), consent withdrawal or patient refusal (n = 14), adverse events of CCRT (n = 12), disease progression (n = 10), and other reason (n = 8).

Efficacy

With a median follow-up time of 50.7 months, there were 349 events in total, 180 in the observation arm and 169 in the consolidation arm. There was no difference in PFS between the two arms, with a median PFS of 8.1 months (95% CI, 7.6 to 8.9 months) in the observation arm and 9.1 months (95% CI, 7.9 to 10.9 months) in the consolidation arm (hazard ratio [HR], 0.91; 95% CI, 0.73 to 1.12; P = .36; Fig 2A). In subgroup analysis, none of the factors except age (> 60 years old) were significant (Appendix Fig A2, online only).

There were 279 deaths, 145 in the observation arm and 134 in the consolidation arm. Median OS also did not differ between the two arms, with a median OS of 20.6 months (95% CI, 17.6 to 26.3 months) in the observation arm and 21.8 months (95% CI, 17.7 to 24.7 months) in the consolidation arm (HR, 0.91; 95% CI, 0.72 to 1.25; P = .44; Fig 2B).

The overall response rate was 38.4% (with 4.3% complete response) in the observation arm versus 43.1% (with 2.9% complete response) in the consolidation arm without a significant difference.
The disease control rate was approximately 58% in both arms (Appendix Table A1, online only).

At the time of this analysis, the sites of treatment failure were known in approximately half of the patients. Both arms showed similar locoregional or distant failure rates with no significant differences. The remaining or contralateral lung was the most common site of the first relapse followed by the brain, pleura, bone, and liver (Appendix Table A2, online only).

Safety

During the CCRT phase, the hematologic toxicities were as expected. In patients assigned to the consolidation arm, there was slightly more febrile neutropenia and grade 3 or 4 neutropenia (Table 3). Table 4 lists the nonhematologic toxicities. During the CCRT phase, esophagitis was observed in 79% of patients with 9.5% grade 3 or 4 toxicities. Grade 3 or 4 infections developed in 6.4% of patients with some treatment-related mortality (TRM). Radiation pneumonitis was less frequently observed, but one patient died of radiation pneumonitis. During the consolidation phase, 2.3% of patients experienced grade 3 or 4 infection, and 1.2% of patients had grade 3 or 4 radiation pneumonitis with some ensuing TRM. The overall TRM rate was 3.6% during the CCRT phase and 2.9% during the consolidation phase.

Exploratory Biomarker Study

The median H scores for ERCC1 (n = 97) and class III β-tubulin (n = 97) were 240 and 30, respectively. ERCC1 expression had no significant correlation with PFS or OS (P = .40 and P = .53, respectively). Class III β-tubulin expression was also not correlated with PFS or OS (P = .97 and P = .44, respectively).

DISCUSSION

Most studies that have investigated the role of CC after CCRT have been small phase I/II trials; few large randomized phase III trials have been conducted. In each trial, there have been differences in patient characteristics, CCRT backbones, or CC regimens, and none of the trials were designed for a specific subset of patients by incorporating molecular biomarkers.18 Our randomized phase III trial, which is the largest reported to date, failed to demonstrate that CC with DP after completing CCRT with the same agents improved survival. This is in line with a recent report on the pooled analysis of 41 studies, which failed to provide evidence that CC yield significant survival benefit for patients with LA-NSCLC.19

While this study was being conducted, a phase III study by the Hoosier Oncology Group (HOG), which included 203 patients using single-agent docetaxel as CC after CCRT, was prematurely terminated as a result of futility analysis. Compared with the HOG study, we had stricter criteria for N2 or N3 disease, which needed to be proven by pathology or PET. More patients were staged by PET in our study than in the HOG study (92% vs 67%, respectively). The most striking difference in study design was the random assignment point. Our patients were randomly assigned before the start of CCRT. We thought patients Events mPFS (95% CI)
CCRT alone 211 180 8.05 (7.56 to 8.90)
CCRT + consolidation 209 169 9.10 (7.92 to 10.94)

Patients Events mOS (95% CI)
CCRT alone 211 145 20.63 (17.58 to 26.28)
CCRT + consolidation 209 134 21.78 (17.71 to 24.74)

Table 3. Hematologic Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CCRT Phase (n = 420)</th>
<th>Observation (n = 171)</th>
<th>Consolidation (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2  Grade 3  Grade 4</td>
<td>Grade 2  Grade 3  Grade 4</td>
<td>Grade 2  Grade 3  Grade 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.9  5.2  0.2</td>
<td>12.9  1.2  2.3</td>
<td>28.3  1.7  0.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.9  2.6  0</td>
<td>2.9  0.6  2.3</td>
<td>7.5  4.6  2.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>NA  0.7  0.2</td>
<td>NA  0  0</td>
<td>NA  1.2  0.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.9  0.5  0</td>
<td>0  1.2  2.3</td>
<td>1.7  0.6  1.2</td>
</tr>
</tbody>
</table>

Abbreviations: CCRT, concurrent chemoradiotherapy; NA, not applicable.
this would result in minimal data loss and less bias. We used DP during CCRT instead of the more common regimen of EP to investigate whether these newer agents were any superior to older ones. Docetaxel has been tested in CCRT with cisplatin in many phase I/II trials with promising response rates,\textsuperscript{16,20–22} and a recent phase III trial showed that CCRT with DP had better efficacy in the early follow-up period.\textsuperscript{23} We also used a DP doublet in the consolidation phase to maximize the effects of additional treatment.

The major obstacle in this trial was that many patients could not complete the three planned cycles of CC, as in other trials.\textsuperscript{19} Approximately one third of the patients (32%) did not even start CC, and only approximately half of the patients could complete ≥ two cycles of CC. Approximately half of the patients failed to start CC because of disease progression or death before the consolidation phase. Another major reason was related to incomplete recovery from the adverse effects of CCRT. A full-dose doublet regimen of CC in our trial might have resulted in poor prognosis in metastatic NSCLC.\textsuperscript{37–39} In contrast, high levels of class III β-tubulin were associated with an adverse prognosis but also seemed to be associated with increased benefit from adjuvant cisplatin/vinorelbine chemotherapy in patients with operable NSCLC.\textsuperscript{40} In our exploratory biomarker study, the expression of ERCC1 and class III β-tubulin was not correlated with either PFS or OS. Until now, no biomarker has been validated to predict benefit or resistance to currently available cytotoxic chemotherapy.\textsuperscript{41}

Nonhematologic toxicities during both the CCRT and consolidation phases were not so severe, perhaps because of the weekly administration of DP. Several phase III trials and a meta-analysis of weekly docetaxel as second-line chemotherapy for advanced NSCLC showed significant benefit in grade 3 to 4 neutropenia compared with administering docetaxel every 3 weeks.\textsuperscript{24–27} Nonhematologic toxicities during the CCRT phase were as expected and similar to conventional CCRT with EP. In brief, CCRT with weekly DP is a feasible regimen with acceptable toxicities.

It is of interest that there was a significant benefit with CC for patients older than age 60 years (HR, 0.72). In a population-based study from National Cancer Institute’s Surveillance, Epidemiology, and End Results database in elderly patients with LA-NSCLC, CCRT alone is associated with the greatest mortality risk compared with either induction chemotherapy or CC with CCRT, suggesting that more gradual strategies may be more appropriate for the elderly population.\textsuperscript{28} In addition, in the combined analysis of five Cancer and End Results database in elderly patients with LA-NSCLC, CCRT has been tested in CCRT with cisplatin in many phase I/II trials with promising response rates,\textsuperscript{16,20–22} and a recent phase III trial showed that CCRT with DP had better efficacy in the early follow-up period.\textsuperscript{23} We also used a DP doublet in the consolidation phase to maximize the effects of additional treatment.

Table 4. Nonhematologic Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CCRT Phase (n = 420)</th>
<th>Observation (n = 171)</th>
<th>Consolidation (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 to 4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Anorexia</td>
<td>70.2</td>
<td>4.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>58.3</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20.7</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.3</td>
<td>1.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>23.3</td>
<td>1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>79.3</td>
<td>9.5</td>
<td>26.9</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>35.5</td>
<td>3.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Infection</td>
<td>17.6</td>
<td>6.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>2.4</td>
<td>0</td>
<td>5.8</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>3.6 (n = 15)</td>
<td>0.0</td>
<td>2.9 (n = 5)</td>
</tr>
</tbody>
</table>

Abbreviation: CCRT, concurrent chemoradiotherapy.

ERCC1 is a component of the nucleotide excision repair pathway, which is essential for the repair of platinum-DNA adducts and is associated with cellular resistance to platinum compounds. Low ERCC1 expression has been correlated with superior PFS and OS in patients with advanced NSCLC treated with cisplatin.\textsuperscript{30–32} In a small-scale retrospective study, immunohistochemistry for ERCC1 was useful for predicting survival in patients with LA-NSCLC receiving CCRT with DP.\textsuperscript{33} The International Adjuvant Lung Cancer Trial Collaborative Group has demonstrated a survival benefit with adjuvant cisplatin-based chemotherapy in patients whose tumors were negative for ERCC1 expression.\textsuperscript{34} However, the ERCC1 immunohistochemistry results were not reproducible.\textsuperscript{35,36} Small comparative studies have also shown that overexpression of class III β-tubulin is correlated with resistance to tubulin-binding agents, taxanes, and vinorelbine and has resulted in poor prognosis in metastatic NSCLC.\textsuperscript{37–39} In contrast, high levels of class III β-tubulin were associated with an adverse prognosis but also seemed to be associated with increased benefit from adjuvant cisplatin/vinorelbine chemotherapy in patients with operable NSCLC.\textsuperscript{40} In our exploratory biomarker study, the expression of ERCC1 and class III β-tubulin was not correlated with either PFS or OS. Until now, no biomarker has been validated to predict benefit or resistance to currently available cytotoxic chemotherapy.\textsuperscript{41}

Given that almost half of the patients could not receive CC after CCRT as a result of early progression and/or toxicities, we need to develop better tolerated regimens without the loss of efficacy. Several new agents are under investigation. PROCLAIM, a phase III study of pemetrexed, cisplatin, and RT followed by consolidation pemetrexed versus EP and RT followed by a CC of choice in patients with stage III NSCLC of nonsquamous histology, was prematurely terminated based on the planned interim futility analysis.\textsuperscript{42} The role of cetuximab is being evaluated in the Radiation Therapy Oncology Group 0617 trial, which randomly assigned patients to standard-dose or high-dose RT or carboplatin and paclitaxel alone, with or without cetuximab concurrent with RT. The inferior results of high-dose RT were already presented, and the effect of cetuximab awaits further follow-up.\textsuperscript{43} L-BLP25 is a MUC1 antigen-specific cancer immunotherapy. A phase III trial (START [Stimulating Targeted Antigenic Response to Non-Small-Cell Lung Cancer]) investigating L-BLP25 in patients who have finished CCRT was completed. L-BLP25 maintenance therapy, however, did not significantly prolong OS.\textsuperscript{44} Given the
high locoregional failure and the presence of distant metastases, newer RT techniques are needed including hypofractionation, stereotactic body RT, adaptive RT, or proton therapy.

In summary, this study confirms that the current strategy of consolidation treatment with cytotoxic chemotherapy after CCRT does not improve survival in patients with LA-NSCLC. In future trials, CCRT without CC should remain the reference arm. Given that distant failure is the most common pattern of failure after CCRT in LA-NSCLC and the treatment outcome remains poor, we strongly believe that the concept of consolidation therapy needs to be further explored using less toxic, better tolerated agents.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES


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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

### Table A1. Overall Response to CCRT

<table>
<thead>
<tr>
<th>Response</th>
<th>CCRT Alone (n = 211)</th>
<th>CCRT + Consolidation (n = 209)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9 (4.3)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>72 (34.1)</td>
<td>84 (40.2)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>43 (20.4)</td>
<td>32 (15.3)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>44 (20.9)</td>
<td>44 (21.1)</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>43 (24.1)</td>
<td>43 (22.1)</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>81 (38.4)</td>
<td>90 (43.1)</td>
<td>.3297</td>
</tr>
<tr>
<td>DCR</td>
<td>124 (58.8)</td>
<td>122 (58.4)</td>
<td>.9346</td>
</tr>
</tbody>
</table>

Abbreviations: CCRT, concurrent chemoradiotherapy; CR, complete response; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

*No. of patients with unconfirmed CR or PR.

### Table A2. Pattern of Failure

<table>
<thead>
<tr>
<th>Treatment Failure</th>
<th>CCRT Alone (n = 211)</th>
<th>CCRT + Consolidation (n = 209)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Patients with treatment failure</td>
<td>115 (54.5)</td>
<td>112 (53.6)</td>
<td></td>
</tr>
<tr>
<td>Locoregional failure</td>
<td>57 (49.6)</td>
<td>50 (44.6)</td>
<td>.42</td>
</tr>
<tr>
<td>Distant failure</td>
<td>50 (43.5)</td>
<td>56 (50.0)</td>
<td>.55</td>
</tr>
<tr>
<td>Local and distant failure</td>
<td>8 (7.0)</td>
<td>6 (5.4)</td>
<td>.59</td>
</tr>
<tr>
<td>Site of distant failure*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Pleura</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CCRT, concurrent chemoradiotherapy.

*Select sites; multiple sites in some patients.

---

**Fig A1.** Immunohistochemical staining of ERCC1 and class III β-tubulin protein in lung cancer tissues. Examples of the expression of each protein are shown. (A) ERCC1 H score of 300. (B) ERCC1 H score of 40. (C) Class III β-tubulin H score of 280. (D) Class III β-tubulin H score of 20.
### Table: Subgroup Analysis for Progression-Free Survival (PFS)

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Sex</th>
<th>Pathology</th>
<th>ECOG PS</th>
<th>FEV1</th>
<th>Stage</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 60</td>
<td>Male</td>
<td>Squamous</td>
<td>0</td>
<td>≥ 2.0 L</td>
<td>IIIA</td>
<td>195</td>
<td>1.15</td>
<td>0.85 to 1.55</td>
<td>.376</td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>Female</td>
<td>Nonsquamous</td>
<td>1</td>
<td>&lt; 2.0 L</td>
<td>IIIB</td>
<td>225</td>
<td>0.72</td>
<td>0.53 to 0.97</td>
<td>.030</td>
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</tr>
<tr>
<td>Male</td>
<td>347</td>
<td>0.92</td>
<td>0.73 to 1.15</td>
<td>0.451</td>
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<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>73</td>
<td>0.89</td>
<td>0.52 to 1.53</td>
<td>.671</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Squamous</td>
<td>135</td>
<td>0.88</td>
<td>0.60 to 1.30</td>
<td>.523</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Nonsquamous</td>
<td>271</td>
<td>0.94</td>
<td>0.72 to 1.22</td>
<td>.639</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>99</td>
<td>1.08</td>
<td>0.69 to 1.71</td>
<td>.731</td>
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<tr>
<td>1</td>
<td>288</td>
<td>0.86</td>
<td>0.67 to 1.11</td>
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<tr>
<td>≥ 2.0 L</td>
<td>287</td>
<td>0.88</td>
<td>0.60 to 1.29</td>
<td>.526</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.0 L</td>
<td>133</td>
<td>0.93</td>
<td>0.72 to 1.20</td>
<td>.586</td>
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<td></td>
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<tr>
<td>IIIA</td>
<td>93</td>
<td>1.17</td>
<td>0.74 to 1.84</td>
<td>.498</td>
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<tr>
<td>IIIB</td>
<td>325</td>
<td>0.85</td>
<td>0.67 to 1.08</td>
<td>.184</td>
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<tr>
<td>Total</td>
<td>420</td>
<td>0.91</td>
<td>0.73 to 1.12</td>
<td>.360</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Fig A2.** Subgroup analysis for progression-free survival (PFS). ECOG PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 second; HR, hazard ratio.