

CLINICAL INVESTIGATION

Lung

COMPARISON OF OUTCOMES FOR PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER TREATED WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION VS. CONCURRENT CHEMORADIATION ALONE

EUGENE H. HUANG, M.D.,* ZHONGXING LIAO, M.D.,* JAMES D. COX, M.D.,* THOMAS M. GUERRERO, M.D., PH.D.,* JOE Y. CHANG, M.D., PH.D.,* MELINDA JETER, M.D.,* YERKO BORGHIERO, M.D.,* XIONG WEI, M.D.,* FRANK FOSSELLA, M.D.,† ROY S. HERBST, M.D., PH.D.,† GEORGE R. BLUMENSCHEN, JR., M.D.,† CESAR MORAN, M.D.,‡ PAMELA K. ALLEN, PH.D.,* AND RITSUKO KOMAKI, M.D.*

Departments of *Radiation Oncology, †Thoracic/Head and Neck Medical Oncology, and ‡Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Purpose: To retrospectively compare outcomes for patients with unresectable locally advanced non-small-cell lung cancer (NSCLC) treated at our institution with concurrent chemoradiation with or without induction chemotherapy.

Methods and Materials: We retrospectively analyzed 265 consecutive patients who received definitive treatment with three-dimensional conformal radiation and concurrent chemotherapy. Of these, 127 patients received induction chemotherapy before concurrent chemoradiation.

Results: The two groups of patients (with induction vs. without induction chemotherapy) were similar in age, performance status, weight loss, histology, grade, and stage. Patients who received induction chemotherapy had better overall survival (median, 1.9 vs. 1.4 years; 5-year rate, 25% vs. 12%; $p < 0.001$) and distant metastasis-free survival (5-year rate, 42% vs. 23%; $p = 0.021$). Locoregional control was not significantly different between the two groups. Multivariate analysis showed that induction chemotherapy was the most significant factor affecting overall survival, with a hazard ratio of 0.55 (95% confidence interval 0.40–0.75; $p < 0.001$). A planned subgroup analysis showed that induction chemotherapy was associated with a significant overall survival benefit for patients with adenocarcinoma or large-cell carcinoma (5-year rate, 24% vs. 8%; $p = 0.003$) but not for those with squamous cell carcinoma. A multivariate analysis of patients with adenocarcinoma or large-cell carcinoma confirmed that induction chemotherapy was the most significant factor associated with better overall survival, with a hazard ratio of 0.47 (95% confidence interval, 0.28–0.78; $p = 0.003$).

Conclusion: Our retrospective analysis suggests that in combination with concurrent chemoradiation, induction chemotherapy may provide a small but significant survival benefit for patients with unresectable locally advanced adenocarcinoma or large-cell carcinoma of the lung. © 2007 Elsevier Inc.

Non-small-cell lung cancer, Induction chemotherapy, Chemoradiation, Adenocarcinoma.

INTRODUCTION

Many randomized trials have established the importance of integrating chemotherapy with radiation for the treatment of unresectable locally advanced non-small-cell lung cancer (NSCLC). Initially, studies showed that the addition of induction chemotherapy to radiotherapy could reduce distant metastases and increase median survival from 10 to 14 months without compromising local control (1, 2). Subsequent trials demonstrated that giving chemotherapy concur-

rently with radiation could further improve upon the results from sequential treatment by increasing the median survival to 17 months with greater local control (3–5). The combined benefits of sensitizing tumor cells to radiation and early treatment of micrometastatic disease have established concurrent chemoradiation as the current standard of care for unresectable NSCLC in patients with good performance status (6).

Despite these recent advances, the prognosis for these patients remains poor, with a high rate of metastasis and a

Reprint requests to: Ritsuko Komaki, M.D., Department of Radiation Oncology – Unit 97, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Tel: (713) 563-2300; Fax: (713) 563-2331; E-mail: rkomaki@mdanderson.org

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5-year survival rate of approximately 15% (3–5). To improve upon the standard of concurrent chemoradiation, many investigators are revisiting the potential benefit of adding induction chemotherapy to this treatment strategy. However, treatment recommendations regarding this approach remain a subject of considerable debate. Because of the lack of definitive data, the American Society of Clinical Oncology did not establish a consensus in its current guidelines for unresectable NSCLC on whether to add induction chemotherapy to concurrent chemoradiation (6). The purpose of this study was to evaluate the efficacy of this approach by comparing the outcomes for patients with unresectable locally advanced NSCLC treated using induction chemotherapy followed by concurrent chemoradiation vs. concurrent chemoradiation alone.

METHODS AND MATERIALS

Patient population and treatment details

We retrospectively reviewed the medical and radiation records of all patients with NSCLC who were treated from October 1998 to November 2003 in the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center (Houston, TX). Patients were included in this study if they had a newly diagnosed locally advanced NSCLC that was treated definitively with three-dimensional conformal radiotherapy (3D-CRT) and concurrent chemotherapy. This retrospective study was approved by the institutional review board, and informed consent was waived. Compliance with Health Insurance Portability and Accountability Act regulations was strict.

We identified 265 patients who met these criteria. Of these, 127 (48%) were initially treated with induction chemotherapy for two or three cycles using a dual-agent regimen. The majority ($n = 121$) were treated with platinum and taxane-based regimens (cisplatin or carboplatin, and paclitaxel or docetaxel). The other 6 patients received cisplatin and etoposide ($n = 1$), cisplatin and gemcitabine ($n = 2$), or gemcitabine and vinorelbine ($n = 3$). Induction chemotherapy was not a randomized variable. The decision to undergo induction chemotherapy was determined by the patient and his or her physicians.

All 265 patients received 3D-CRT and concurrent chemotherapy, which typically consisted of a weekly platinum- and taxane-based regimen ($n = 165$), weekly platinum and etoposide ($n = 18$), or cisplatin and etoposide for two cycles ($n = 63$). Nineteen patients received a single-agent platinum, taxane, or gemcitabine regimen on a weekly basis. Radiation treatment typically targeted the gross tumor volume (GTV) and the involved lymph node stations. Uninvolved lymph node stations were not electively irradiated. The clinical target volume (CTV) was defined as the GTV plus an 8-mm margin, and the planning target volume (PTV) was defined as the CTV plus a 10- to 15-mm margin. The radiation dose was prescribed to cover at least 95% of the PTV. Patients received radiation treatment daily in 1.8- or 2-Gy fractions ($n = 183$), or twice-daily in 1.2-Gy fractions ($n = 82$). The median dose delivered was 63 Gy (range, 34.8–72 Gy). Nine patients included in this analysis were unable to complete radiation treatment and received doses less than 60 Gy because of toxicity or disease progression during radiation.

After concurrent chemotherapy and radiation, 24 of the patients who did not receive induction chemotherapy were treated with

adjuvant chemotherapy. These regimens changed over the period of time and consisted of regimens that were platinum-based ($n = 5$), taxane-based ($n = 12$), or both ($n = 7$).

Statistical analysis

The distribution of patient characteristics between the two groups (with induction chemotherapy vs. without induction chemotherapy) was compared using the chi-square test for dichotomized variables and the Mann-Whitney test for the continuous variable of age. The primary endpoint analyzed was overall survival (OS). Secondary endpoints included locoregional control (LRC) and distant metastasis-free survival (DMFS). Locoregional control was defined as being free from any recurrences involving the same lung lobe or any regional lymph nodes (ipsilateral or contralateral hilar, mediastinal, or supraclavicular nodes). All other disease recurrences were considered distant metastases.

The rates of 2- and 5-year OS, LRC, and DMFS were calculated with the Kaplan-Meier method, and comparisons between the two groups were made with the log-rank test (7). A multivariate analysis of OS was performed with a Cox proportional hazards model (7) using both forward and backward stepwise analysis incorporating the following factors: induction chemotherapy, age, weight loss, performance status, histology, grade, combined stage, T stage, N stage, mediastinoscopic staging, positron emission tomography (PET) staging, and twice-daily radiation treatment. All survival statistics were measured from the date of diagnosis. All p values were two-sided, and values ≤ 0.05 were considered significant. A planned subgroup analysis was performed for patients with squamous cell carcinoma vs. adenocarcinoma or large-cell carcinoma.

An unknown number of patients may have been initially started on induction chemotherapy with the intent of proceeding on to definitive concurrent chemoradiation, but subsequently did not receive concurrent chemoradiation owing to early development of metastatic disease during the induction chemotherapy. Because of the retrospective nature of this study, these patients could not be identified and were not included in our study population. However, to evaluate whether this potential selection bias may have affected our results, we repeated our analysis but excluded any patient from the without-induction-chemotherapy group who had an early distant metastasis ($n = 16$) or early death ($n = 7$) within 2 months after finishing concurrent chemoradiation.

RESULTS

The median follow-up was 19 months (range, 3–80 months). Table 1 presents the patient and disease characteristics of the two groups. A greater percentage of patients who received induction chemotherapy had PET as part of their staging workup (64% vs. 36%; $p < 0.001$), and a greater percentage of patients who did not receive induction chemotherapy had twice-daily radiation treatment (47% vs. 13%; $p < 0.001$). These differences reflected the time period in which the patients were treated. In general, induction chemotherapy was used more frequently in more recent years, which coincided with the development of PET scanning in clinical practice. There were no differences between the two groups with respect to age, weight loss, performance status, histology, grade, combined stage, T stage, N stage, or mediastinoscopic staging.

Table 1. Patient and disease characteristics

| Characteristic | Without induction (n = 138) | With induction (n = 127) | p* |
|-----------------------------|--------------------------------|-----------------------------|--------|
| Median age (y) | 63 | 60 | NS |
| Weight loss >10% in 6 mo | 30 (22) | 18 (14) | NS |
| Performance status (ECOG) | | | NS |
| 0 | 29 (21) | 34 (27) | |
| 1 | 104 (75) | 90 (71) | |
| 2 | 5 (4) | 3 (2) | |
| Histology | | | NS |
| Non-small-cell, unspecified | 26 (19) | 32 (25) | |
| Squamous cell carcinoma | 51 (37) | 39 (31) | |
| Adenocarcinoma | 50 (36) | 52 (41) | |
| Large-cell carcinoma | 8 (6) | 4 (3) | |
| Other | 3 (2) | 0 (0) | |
| Grade | | | NS |
| Well-differentiated | 3 (2) | 5 (4) | |
| Moderately differentiated | 12 (9) | 12 (9) | |
| Poorly differentiated | 80 (58) | 62 (49) | |
| Unspecified | 43 (31) | 48 (38) | |
| Combined stage | | | NS |
| IIA | 0 (0) | 1 (1) | |
| IIB | 2 (1) | 2 (2) | |
| IIIA | 48 (35) | 47 (37) | |
| IIIB | 88 (64) | 77 (61) | |
| T stage | | | NS |
| 0 | 4 (3) | 2 (2) | |
| 1 | 14 (10) | 24 (19) | |
| 2 | 42 (30) | 47 (37) | |
| 3 | 20 (14) | 16 (13) | |
| 4 | 58 (42) | 38 (30) | |
| N stage | | | NS |
| 0 | 11 (8) | 4 (3) | |
| 1 | 3 (2) | 5 (4) | |
| 2 | 72 (52) | 66 (52) | |
| 3 | 52 (38) | 52 (41) | |
| Mediastinoscopic staging | 25 (18) | 23 (18) | NS |
| PET staging | 50 (36) | 81 (64) | <0.001 |
| Twice daily radiation | 65 (47) | 17 (13) | <0.001 |

Abbreviations: NS = not significant; ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography.

Data are presented as number (percentage), unless otherwise specified.

* The Mann-Whitney test was used for the continuous variable of age. All other *p* values were derived with the chi-square test for equality of distributions.

The rates of OS, DMFS, and LRC for the entire group of 265 patients were 41%, 43%, and 57% at 2 years, and 19%, 33%, and 51% at 5 years, respectively. Induction chemotherapy was associated with better OS than concurrent chemoradiation alone (median, 1.9 vs. 1.4 years; 2-year rate, 49% vs. 34%; 5-year rate, 25% vs. 12%; *p* < 0.001) (Fig. 1). In addition, induction chemotherapy was associated with better DMFS (2-year rate, 47% vs. 38%; 5-year rate, 42% vs. 23%; *p* = 0.021) (Fig. 2). Locoregional control was not significantly different between the two groups (5-year rate, 53% with induction vs. 49% without induction; *p* = 0.62). A multivariate Cox regression analysis of factors associated with OS (Table 2) showed that having induction chemo-

therapy was the most significant variable, with a hazard ratio of 0.55 (95% confidence interval [CI] 0.40–0.75; *p* < 0.001). Two other factors found to be significantly associated with better OS were having Stage ≤IIIA disease and having twice-daily radiation treatment. These three factors were identified in both forward and backward stepwise analyses. Of note, having PET as part of the staging workup was not found to be a significant factor associated with OS, DMFS, or LRC in the univariate or multivariate analyses.

A planned subgroup analysis examining the effect of histology on OS showed that induction chemotherapy significantly improved OS for patients with adenocarcinoma or large-cell carcinoma (median, 2.0 vs. 1.4 years; 2-year rate, 48% vs. 34%; 5-year rate, 24% vs. 8%; *p* = 0.003), but not for those with squamous cell carcinoma (*p* = 0.29) (Fig. 3). In patients with adenocarcinoma or large-cell carcinoma, the same three factors as in the entire group were found to be associated with better OS in both forward and backward stepwise multivariate analysis: induction chemotherapy, Stage ≤IIIA disease, and twice-daily radiation treatment (Table 2). Of these, having induction chemotherapy was the most significant factor, with a hazard ratio of 0.47 (95% CI 0.28–0.78; *p* = 0.003). For patients with squamous cell carcinoma, having induction chemotherapy was not a significant factor affecting OS.

To evaluate the potential selection bias that some patients may have begun treatment with induction chemotherapy but did not go on to receive concurrent chemoradiation owing to early development of metastatic disease during induction chemotherapy, we repeated our analysis but excluded any patient from the without-induction-chemotherapy group who had an early distant metastasis (*n* = 16) or death (*n* = 7) within 2 months after finishing concurrent chemoradiation. The results were similar to those in our first analysis. Patients who received induction chemotherapy continued to have better OS than those who did not (median, 1.9 vs. 1.6 years; 2-year rate, 49% vs. 41%; 5-year rate, 25% vs. 14%; *p* = 0.038). The same three factors were found to be significantly associated with better OS on multivariate Cox regression analysis: induction chemotherapy (hazard ratio, 0.65, 95% CI 0.46–0.90; *p* = 0.009), Stage ≤IIIA disease, and twice-daily radiation treatment. A significant survival benefit from having induction chemotherapy was observed in the patients with adenocarcinoma or large-cell carcinoma (median, 2.0 vs. 1.7 years; 2-year rate, 48% vs. 41%; 5-year rate, 24% vs. 10%; *p* = 0.032), but not in those with squamous cell carcinoma (*p* = 0.70). A multivariate analysis of the patients with adenocarcinoma or large-cell carcinoma confirmed that the same factors were associated with OS: induction chemotherapy (hazard ratio, 0.54; 95% CI 0.32–0.92; *p* = 0.022), Stage ≤IIIA disease, and twice-daily radiation treatment.

DISCUSSION

This report presents a single institution's experience with 265 consecutive patients with unresectable NSCLC treated

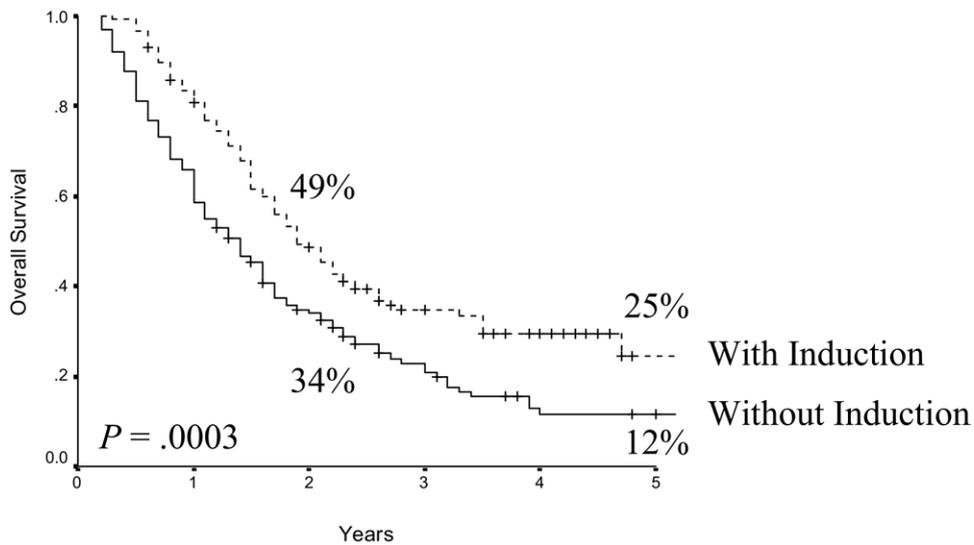


Fig. 1. Overall survival for patients treated with and without induction chemotherapy.

with curative intent using modern radiation techniques and concurrent platinum- and/or taxane-based chemotherapy. The results of this study suggest that adding two or three cycles of induction chemotherapy may improve OS by reducing distant metastases without compromising local control.

Our results for patients treated with concurrent chemoradiation alone were similar to those from the two randomized trials that established this approach as the standard of care. The West Japan Lung Cancer Group (3) and the Radiation

Therapy Oncology Group (RTOG) 94-10 (4) trials both showed that concurrent chemoradiation resulted in a median OS of 17 months. Our analysis demonstrated that adding induction chemotherapy to concurrent chemoradiation may further improve the median survival by at least 3 more months. A multivariate analysis revealed that treatment with induction chemotherapy was the most significant factor associated with OS, resulting in a 5-year rate of 25%, compared with 12% without induction chemotherapy.

One of the most notable findings from our analysis was

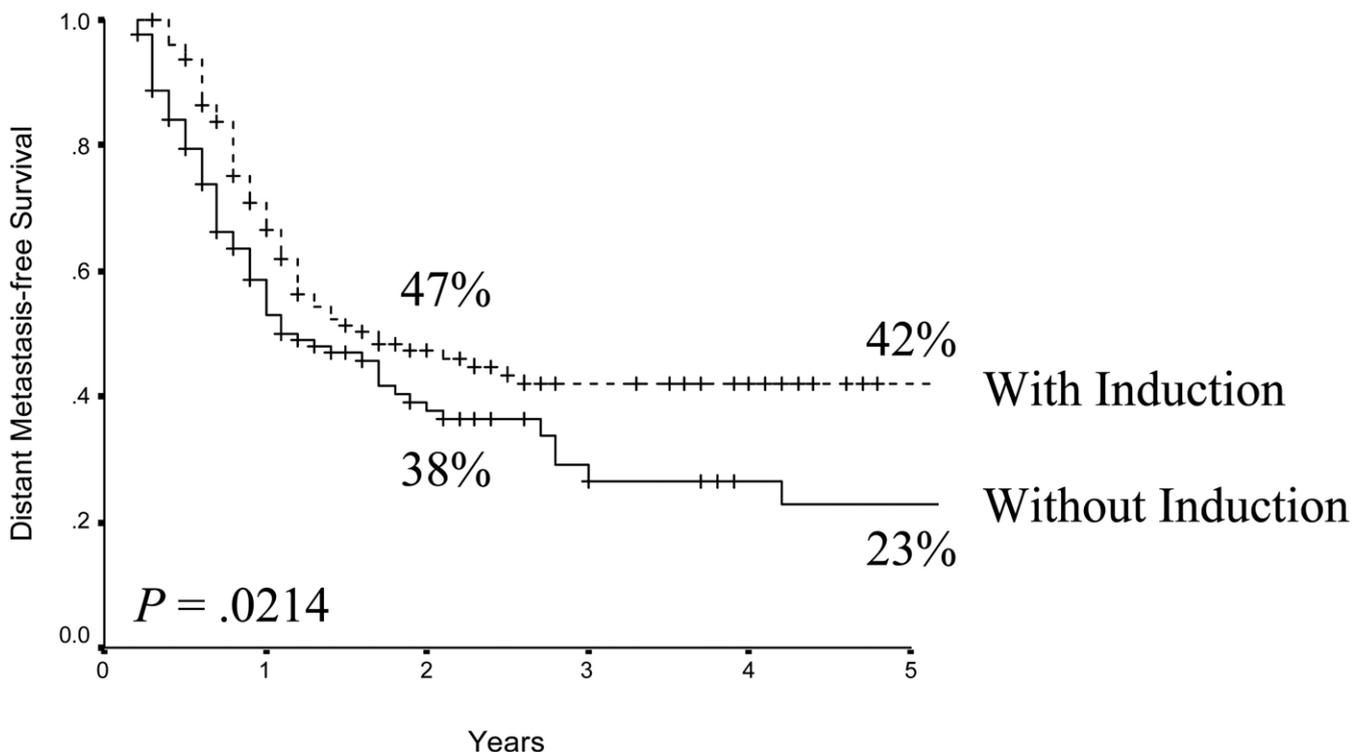


Fig. 2. Distant metastasis-free survival for patients treated with and without induction chemotherapy.

Table 2. Multivariate analysis of factors associated with overall survival

| Factor | Hazard ratio | 95% confidence interval | <i>p</i> |
|--|--------------|-------------------------|----------|
| All patients (<i>n</i> = 265) | | | |
| Induction chemotherapy | 0.55 | 0.40–0.75 | <0.001 |
| Stage ≤IIIA | 0.66 | 0.49–0.89 | 0.007 |
| Twice-daily radiation | 0.71 | 0.51–0.98 | 0.039 |
| Patients with adenocarcinoma or large-cell carcinoma (<i>n</i> = 114) | | | |
| Induction chemotherapy | 0.47 | 0.28–0.78 | 0.003 |
| Twice-daily radiation | 0.59 | 0.35–0.99 | 0.045 |
| Stage ≤IIIA | 0.62 | 0.37–1.05 | 0.078 |

that the survival advantage from adding induction chemotherapy to concurrent chemoradiation applied only to patients with adenocarcinoma or large-cell carcinoma. Interestingly, a similar finding was reported by Komaki *et al.* (8) in an analysis of outcomes from the RTOG 88-08/Eastern Cooperative Oncology Group 4588 trial by histologic cell type. Their intergroup trial compared three treatment arms: 60 Gy of radiation alone, 69.6 Gy of hyperfractionated radiation alone, and sequential induction chemotherapy (cisplatin and vinblastine) followed by 60 Gy of radiation alone. Even though their trial differed from ours in that it did not include concurrent chemotherapy with the radiation treatment, it nonetheless demonstrated a similar finding: adding induction chemotherapy provided a significant survival benefit only for patients with nonsquamous cell carcinoma (most of whom had adenocarcinoma or large-cell carcinoma).

This observation emphasizes the importance of giving multidisciplinary care and tailoring treatment strategies to individual patients. For patients with an unresectable squamous cell carcinoma with a greater risk for locoregional invasion, induction chemotherapy may not provide any significant advantages; instead, this subset of patients may benefit from pursuing other strategies, such as adding consolidation chemotherapy (9). However, for patients with adenocarcinoma or large-cell carcinoma, induction chemotherapy followed by concurrent chemoradiation may provide a small but significant OS benefit (hazard ratio, .47) by allowing the earliest possible treatment of micrometastases using full systemic doses of chemotherapy. This approach is consistent with the pathogenesis of adenocarcinomas, which have a propensity for lymphatic spread and hematogenous metastases greater than that of squamous cell carcinomas by as much as 20% (10, 11). In the future, individualized treatment approaches based on factors beyond histology and staging, such as screening for mutations in the epidermal growth factor receptor gene (12), should be applied to this inhomogeneous patient population to maximize the potential benefit of molecular targeting agents and other promising treatment strategies.

Other investigators have also explored the question of

whether adding induction chemotherapy to concurrent chemoradiation may improve clinical outcomes. The randomized Phase II Locally Advanced Multi-Modality Protocol (LAMP) was inconclusive in answering this question using a control arm of sequential induction chemotherapy followed by radiation alone for comparison (13). One of the experimental arms in this trial used induction carboplatin and paclitaxel followed by radiation given concurrently with weekly carboplatin and paclitaxel. Compared with the sequential chemotherapy arm and the consolidation chemotherapy arm, the induction chemotherapy arm had slightly higher numbers of patients with negative prognostic factors: age >70 years, male sex, performance status <80, weight loss >5%, and nonsquamous cell histology. Although the difference for each of these parameters was only a few percentage points, the fact that this arm had patients with consistently worse prognostic factors could have, in aggregate, resulted in a worse outcome. This induction chemotherapy treatment arm accrued poorly, with only 74 patients, and the LAMP trial closed early when results from the West Japan Lung Cancer Group and RTOG 94-10 trials established concurrent chemoradiation as the standard of care. The Cancer and Leukemia Group B recently presented the results of its Phase III randomized trial (39801) in abstract form (14). This trial directly addressed the question of whether induction chemotherapy adds any benefit to concurrent chemoradiation by randomizing 366 patients to receive concurrent chemoradiation (carboplatin and paclitaxel) vs. 2 cycles of induction chemotherapy (carboplatin and paclitaxel) followed by concurrent chemoradiation. Although the median OS showed a clear trend favoring induction chemotherapy (14 vs. 11 months), this difference was not significant, and the outcomes of both arms were below historical expectations. Although the abstract itself did not specifically address the issue of histologic cell types, it would be interesting to know whether there was any significant benefit in the subset of patients with adenocarcinoma or large-cell carcinoma.

Another interesting finding from our study was that having accelerated hyperfractionated radiation treatment (69.6 Gy in 58 fractions over 29 days) may have conferred a small but significant survival benefit (hazard ratio, .71). This observation is consistent with previously published data from our institution, which showed that twice-daily radiation significantly improved outcomes, primarily by increasing locoregional tumor control (15). The rationale for using accelerated hyperfractionation to reduce tumor cell repopulation was initially validated with some success in small-cell lung cancer (16) and later in NSCLC using a more intensive regimen of radiation three times per day (17, 18). A secondary analysis of the RTOG 94-10 trial for NSCLC also showed that twice-daily accelerated hyperfractionation with concurrent chemotherapy significantly reduced the rate of locoregional progression compared with once-daily radiation with concurrent chemotherapy, especially for the subset of patients with squamous cell carcinoma (19). This observation reinforces the hypothesis that patients with locally

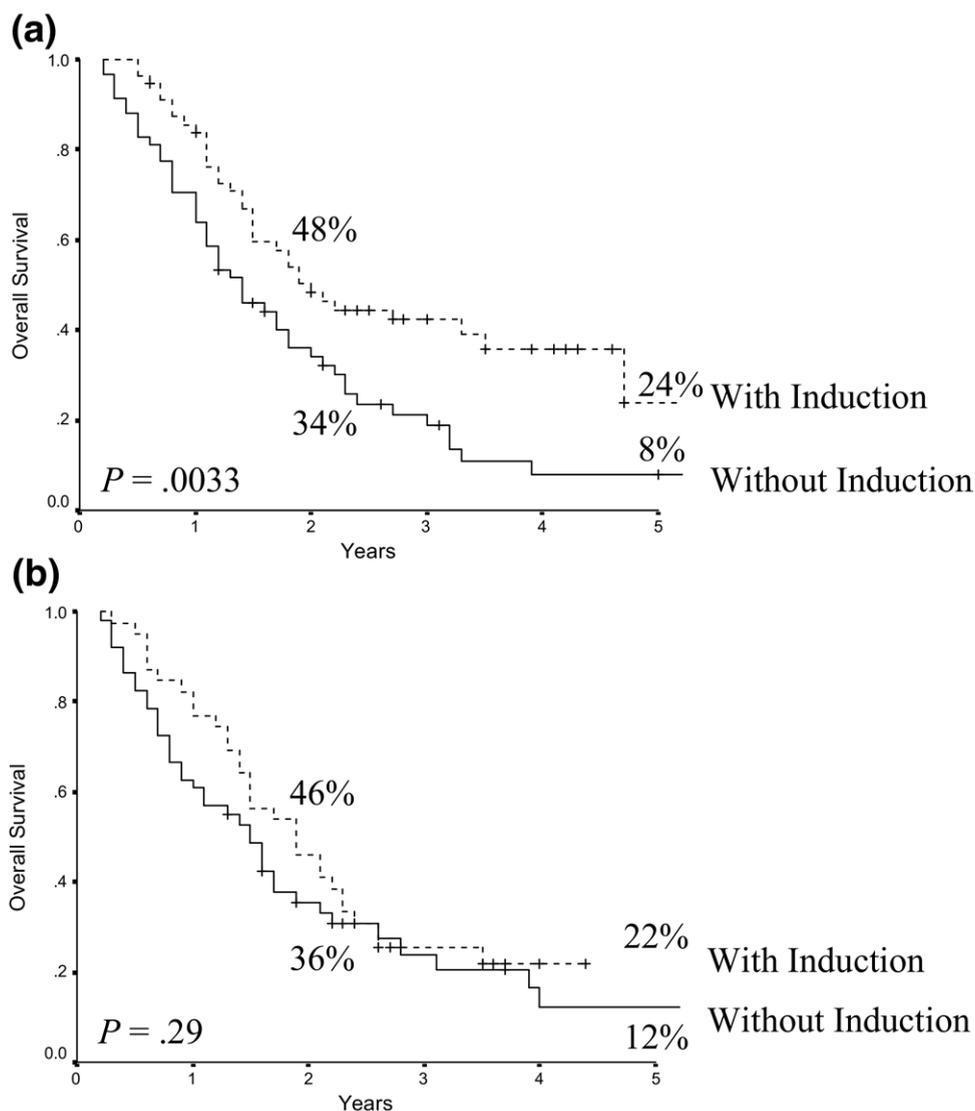


Fig. 3. Overall survival for patients with (a) adenocarcinoma and large-cell carcinoma treated with and without induction chemotherapy, and (b) squamous cell carcinoma treated with and without induction chemotherapy.

invasive carcinomas of squamous cell histology may benefit from a more intensive locoregional treatment regimen given up front. In contrast to our study, the RTOG 94-10 trial did not find a statistically significant survival benefit with accelerated hyperfractionation (4). A crucial difference between our study and RTOG 94-10 is that all of the patients in our study were treated with 3D-CRT instead of conventional radiation technique. By improving dose delivery to the tumor target and limiting toxicity to the normal tissues (even more important given the increased toxicity from concurrent chemotherapy), 3D-CRT may have allowed us to maximize the potential benefit of accelerated hyperfractionation and realize a difference in survival outcomes.

It is important to recognize the limitations of our retrospective study. Even though the two groups were relatively balanced with respect to known prognostic factors, the decision to undergo induction chemotherapy was not a randomized variable and was therefore subject to selection

biases. Foremost, an unknown number of patients may have begun treatment with induction chemotherapy with definitive intent but did not go on to receive concurrent chemoradiation owing to early development of progressive disease or death during the induction chemotherapy. Prospective trials of induction chemotherapy have reported that approximately 6–12% of patients may develop progression of disease (local or distant) or an early death (from disease, toxicity, or any unknown cause) during or immediately after their induction chemotherapy (18, 20). To evaluate whether this potential selection bias may have affected our findings, we repeated our analysis but excluded patients from the without-induction-chemotherapy group who had an early distant metastasis or early death within 2 months of finishing concurrent chemoradiation. Although this analysis confirmed the conclusions from our primary analysis, it is possible that there are other selection biases we could not take into account. In addition, we intentionally focused our

analyses on the endpoint of OS, rather than local recurrence or distant metastasis, to avoid the potential confounding factor that some patients died without any documented disease progression or recurrence. Without an autopsy of these patients, a more specific cause of death cannot be determined. Finally, our analysis is subject to recency bias because the use of induction chemotherapy was generally used more frequently in the more recent years. Although the two groups were similar in stage, performance status, and other known prognostic factors,

it is possible that there are other biases that we did not take into account.

In conclusion, the addition of induction chemotherapy to concurrent chemoradiation was associated with a small but significant survival benefit for patients with unresectable locally advanced NSCLC. On the basis of our retrospective analysis of patients treated at our institution, induction chemotherapy followed by concurrent chemoradiation should be considered in the treatment strategies for patients with adenocarcinoma or large-cell carcinoma of the lung.

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