Original Article

# A Pooled Analysis of Individual Patient Data From National Clinical Trials Network Clinical Trials of Concurrent Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer in Elderly Patients Versus Younger Patients

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**BACKGROUND:** Platinum and etoposide with thoracic radiation followed by prophylactic cranial irradiation constitute the standard treatment for limited-stage small cell lung cancer (LS-SCLC). Many patients with LS-SCLC are elderly with comorbidities. **METHODS:** Individual patient data were collected from 11 phase 2 or 3 trials for LS-SCLC conducted by the National Clinical Trials Network and activated from 1990 to 2010. The primary endpoint was overall survival (OS); the secondary endpoints were progression-free survival (PFS), the rate of severe adverse events, and off-treatment reasons. The outcomes were compared for patients 70 years old or older (elderly patients) and patients younger than 70 years (younger patients). **RESULTS:** Individual patient data from 1049 younger patients (81%) and 254 elderly patients (19%) were analyzed. In the multivariate model, elderly patients, in comparison with younger patients, had worse OS (hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.18-1.63; median OS for elderly patients, 17.8 months; OS for younger patients, 23.5 months) and worse PFS (HR, 1.19; 95% CI, 1.03-1.39; median PFS for elderly patients, 10.6 months; median PFS for younger patients, 12.3 months). Elderly patients, in comparison with younger patients, experienced more grade 5 adverse events (8% vs 3%; $P < .01$) and more grade 3 or higher dyspnea (11% vs 7%; $P = .03$) but less grade 3 or higher esophagitis/dysphagia (14% vs 19%; $P = .04$) and less grade 3 or higher vomiting (11% vs 17%; $P = .01$). Elderly patients completed treatment less often, discontinued treatment because of adverse events and patient refusal more frequently, and died during treatment more frequently. **CONCLUSIONS:** Elderly patients with LS-SCLC have worse PFS and OS and more difficulty in tolerating therapy. Future trials should incorporate assessments of elderly patients, novel monitoring of adverse events, and more tolerable radiation and systemic therapies. ***Cancer* 2018;000:000-000**. © *2018 American Cancer Society.*

**KEYWORDS:** adverse events related to age, chemotherapy, clinical trial, small cell lung cancer, thoracic radiation therapy.

## INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States, and approximately 15% of patients have the small cell lung cancer (SCLC) subtype.[1,2] For patients with limited-stage small cell lung cancer (LS-SCLC), concurrent chemoradiotherapy followed by prophylactic cranial irradiation (PCI) with curative intent is the standard therapy.[3] The median overall survival (OS) observed with concurrent chemoradiotherapy in recent phase 3 trials was 25 to 30 months, and the 5-year OS rate was 25% to 35%.[4,5] However, the trial eligibility criteria limited enrollment to a carefully selected patient population, and elderly patients are underrepresented in lung cancer clinical trials.[6] Clinicians have concerns about the ability of elderly patients to tolerate concurrent chemoradiotherapy and the frequency of severe

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adverse events. Clinicians rely on subset analyses of elderly patients from clinical trials to estimate the efficacy and the frequency of adverse events or to extrapolate the benefit of the study population to elderly and frailer patients.

Most patients with SCLC have a history of tobacco use, are elderly, and have significant comorbidities.[7] Previous retrospective and subset studies have investigated the outcomes of elderly patients, defined as patients 70 years old or older, with LS-SCLC treated with chemoradiotherapy in clinical trials.[8–11] However, only 13% to 21% of the patients enrolled in these trials were 70 years old or older, and these subsets were small (range, 33-88). The small sample size limits the interpretation of the previous analyses. The US National Cancer Institute's National Clinical Trials Network (NCTN) performed clinical trials investigating concurrent chemoradiotherapy for LS-SCLC. These trials were widely available and enrolled patients at both community and academic centers. We investigated the outcomes as assessed by the OS, progression-free survival (PFS), and adverse events of patients enrolled in NCTN trials of concurrent chemoradiotherapy for LS-SCLC.

## MATERIALS AND METHODS

Data sharing agreements with the relevant cooperative groups were developed, and individual patient data were obtained for patients with non–small cell lung cancer and SCLC treated in NCTN trials from 1990 to 2012. A centralized database was developed, and for this analysis, individual patient data were restricted to trials of concurrent chemoradiotherapy for LS-SCLC. We reviewed the study protocols and final publications for inclusion, and only trials that included concurrent chemoradiotherapy were included. We defined patients younger than 70 years as younger and patients 70 years old or older as elderly because this age cutoff was used in previous retrospective analyses of chemoradiotherapy for patients with LS-SCLC.[9–11] The primary endpoint was OS, and the secondary endpoints were PFS, the rate of severe adverse events, and off-treatment reasons. OS was defined as the time between randomization/registration and death from any cause. PFS was defined as the time between randomization/registration and disease progression or death (whichever came first). Severe adverse events were defined as grade 3 or higher with the National Cancer Institute's Common Terminology Criteria for Adverse Events. We compared individual grade 3 or higher adverse events and adverse events of all grades in elderly or younger patients (excluding leukopenia/lymphopenia). The adverse events were for the entire study treatment and included the chemoradiotherapy and chemotherapy-alone portions of the treatment. The study team assessed the off-treatment reasons, which were reported as part of the protocol. Off-treatment reasons reported included treatment completion, adverse events, disease progression, patient refusal of further treatment, death during treatment, treatment never started, development of other disease, and no response to treatment. Off-treatment reasons not mentioned here were categorized as other. Grade 5 adverse events included all fatal events whether related to treatment, comorbidity, or intercurrent illness. The classification of treatment-related death was based on the study team's attribution of the cause of death to the treatment; this was collected as a component of the study protocol.

### *Statistical Methods*

Baseline patient characteristic distributions between the 2 age groups were tested with a chi-square test for categorical variables and with the Kruskal-Wallis test for continuous variables.[12,13] OS and PFS analyses of the 2 age groups were evaluated with Kaplan-Meier curves, and differences were tested with a log-rank test.[14,15] Univariate and multivariate frailty Cox models were then fitted to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS; the heterogeneity between trials was accounted as frailty.[16,17] For multivariate frailty Cox models, the candidate covariates were as follows: age group, sex, race, weight loss, performance status, body mass index, prior chemotherapy or not, prior surgery or not, number of chemotherapy agents, and recent trial or not (the first patient was enrolled in the trial before January 1, 1996). We selected the date of January 1, 1996, for this exploratory analysis to divide the patients into approximately equal cohorts. Because an age effect was of primary interest, it was included in all multivariate models after stepwise selection. For OS, the covariates selected into the final model were age group, sex, race, weight loss, performance status, body mass index, prior surgery or not, number of chemotherapy agents, and recent trial or not. For PFS, the covariates selected into the final model were age group, sex, race, weight loss, performance status, and body mass index.

Adverse events were categorized into 7 categories based on their grade (≥3, ≥4, or 5) and type (hematologic or nonhematologic). Grade 3 or higher adverse events with a frequency ≥ 2% were compared between age groups with a chi-square test. Reasons for treatment

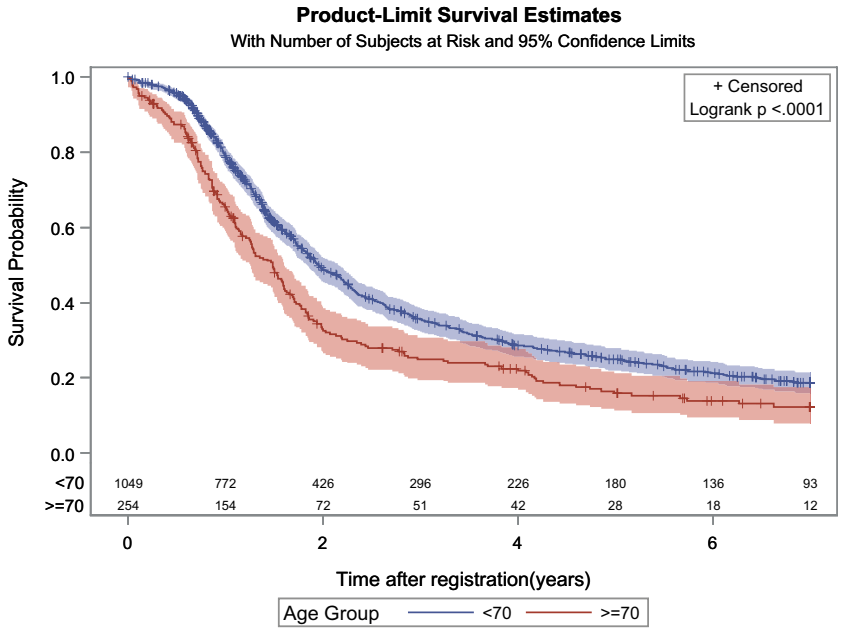


**Figure 1.** Kaplan-Meier curves for overall survival for elderly (age ≥ 70 years) and younger patients (age < 70 years).

discontinuation in the 2 groups were summarized in categories and, for each category, were compared with Fisher's exact test or a chi-square test.[12] All *P* values were 2-sided, and statistical significance was defined as $P < .05$. A sensitivity analysis for the age cutoff of 65 years was performed with the same methodologies. We performed an exploratory analysis dividing the patients into 3 age cohorts (<50, ≥50 to <70, and ≥70 years).

The Duke University institutional review board approved this study. The statistical software was SAS (version 9.4; SAS Institute, Cary, North Carolina).

## RESULTS

Individual patient data from 1303 patients enrolled in 11 trials were included in the analysis (Supporting Fig. 1).[18–28] The trials enrolled patients between 1993 and 2006. All the trials used chemotherapy with cisplatin or carboplatin with concurrent thoracic radiation, most investigated the integration of a novel agent (eg, tamoxifen, topotecan, paclitaxel, irinotecan, or tirapazamine), and all permitted PCI at the discretion of the investigator. Two of the 11 trials were phase 3 trials, and 9 were phase 2 trials; the trials ranged in size from 58 to 324 patients (Supporting Table 1). Nine of the 11 trials included cisplatin-based therapy.

Of the 1303 patients, 1049 patients were younger than 70 years (81%), and 254 were 70 years old or older (19%). The majority of the patients were male and white and did not have any weight loss (Supporting Table 2). There was an imbalance in the performance status ($P = .02$). Among patients younger than 70 years, 49% had a performance status of 0, and 45% had a performance status of 1. Among patients 70 years old or older, 39% had a performance status of 0, and 53% had a performance status of 1. Among patients younger than 70 years, 94% had a performance status of 0 or 1; among

**TABLE 1.** Rate of Grade 3 or Higher AEs Among Older (Age ≥ 70 Years) and Younger Patients (Age < 70 Years)

| AE Category | Age ≥ 70 y (n = 254) | Age < 70 y (n = 1049) | P[a] |
|---|---|---|---|
| All AEs, grade ≥ 3 | 83% (n = 212) | 82% (n = 855) | .47 |
| Hematologic AEs, grade ≥ 3 | 62% (n = 158) | 61% (n = 636) | .64 |
| Nonhematologic AEs, grade ≥ 3 | 54% (n = 136) | 52% (n = 550) | .75 |
| All AEs, grade ≥ 4 | 62% (n = 157) | 50% (n = 527) | <.01 |
| Hematologic AEs, grade ≥ 4 | 50% (n = 128) | 41% (n = 428) | <.01 |
| Nonhematologic AEs, grade ≥ 4 | 24% (n = 61) | 21% (n = 218) | .26 |
| AEs, grade 5 | 8% (n = 20) | 3% (n = 32) | <.01 |
| Treatment-related deaths[b] | 6% (n = 9) | 4% (n = 23) | .22 |

Abbreviation: AE, adverse event.
[a]Chi-square tests were used for AE comparisons.
[b]Treatment-related death data were available for only 7 trials (n = 729).

**TABLE 2.** Rates of Grade 3 or Higher Nonhematologic and Hematologic Adverse Events With a Frequency ≥ 2% in Older (Age ≥ 70 Years) and Younger Patients (Age < 70 Years)

| Adverse Event | Age ≥ 70 y (n = 254) | Age < 70 y (n = 1049) | P[a] |
|---|---|---|---|
| Anemia | 19% (n = 49) | 20% (n = 211) | .77 |
| Anorexia | 9% (n = 22) | 9% (n = 97) | .77 |
| Constipation | 2% (n = 4) | 1% (n = 12) | .58 |
| Dehydration | 7% (n = 19) | 7% (n = 69) | .61 |
| Diarrhea | 6% (n = 15) | 4% (n = 46) | .30 |
| Dyspnea | 11% (n = 27) | 7% (n = 70) | .03 |
| Esophagitis/ dysphagia | 14% (n = 35) | 19% (n = 203) | .04 |
| Fatigue | 13% (n = 34) | 10% (n = 104) | .11 |
| Hyponatremia | 3% (n = 4) | 3% (n = 34) | .16 |
| Hypotension | 3% (n = 8) | 3% (n = 33) | 1.00 |
| Nausea | 18% (n = 48) | 22% (n = 229) | .15 |
| Neutropenia | 56% (n = 142) | 52% (n = 549) | .31 |
| Pain | 7% (n = 17) | 8% (n = 79) | .65 |
| Pneumonitis/ pulmonary infiltrates | 2% (n = 4) | 1% (n = 6) | .10 |
| Vomiting | 11% (n = 28) | 17% (n = 183) | .01 |

[a]Chi-square tests were used for adverse event comparisons.

patients 70 years old or older, 92% had a performance status of 0 or 1.

In univariate and multivariate Cox frailty models, elderly patients, compared with younger patients, experienced worse OS (HR in the univariate model, 1.40; 95% CI, 1.20-1.65; $P < .01$; HR in the multivariate model, 1.38; 95% CI, 1.18-1.63; $P < .01$). The median OS durations observed in the elderly and younger patients were 17.8 and 23.5 months, respectively (Fig. 1). In univariate and multivariate Cox frailty models, elderly patients, compared with younger patients, experienced worse PFS (HR in the univariate model, 1.23; 95% CI, 1.06-1.43; $P < .01$; HR in the multivariate model, 1.19; 95% CI, 1.03-1.39; $P = .02$). The median PFS durations for elderly and younger patients were 10.6 and 12.3 months, respectively (Fig. 2).

Elderly patients, compared with younger patients, experienced similar frequencies of grade 3 or higher adverse events ($P = .47$), grade 3 or higher hematologic adverse events ($P = .64$), and grade 3 or higher nonhematologic adverse events ($P = .75$; Table 1). Elderly patients, compared with younger patients, experienced more grade 4 or higher adverse events ($P < .01$) and grade 4 or higher hematologic adverse events ($P < .01$) but had a similar frequency of grade 4 or higher nonhematologic adverse events ($P = .26$). Elderly patients experienced more grade 5 adverse events (deaths regardless of cause; 8% vs 3%; $P < .01$). When the specific adverse events observed in ≥2% of the patients were analyzed, elderly patients, compared with younger patients, experienced more grade 3 or higher dyspnea (11% vs 7%; $P = .03$) and less esophagitis/ dysphagia (14% vs 19%; $P = .04$) and vomiting (11% vs 17%; $P = .01$; Table 2). When adverse events of all grades

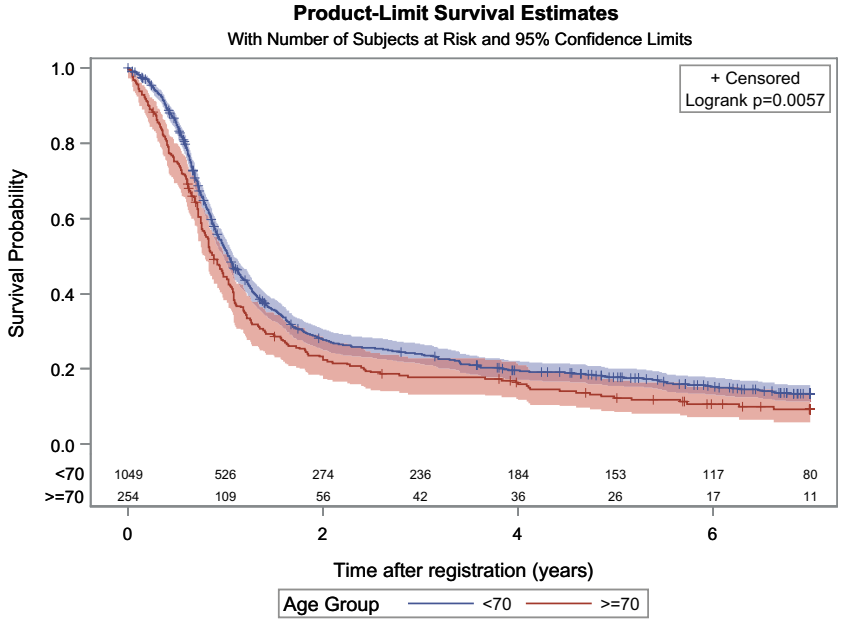


**Figure 2.** Kaplan-Meier curves for progression-free survival for elderly (age ≥ 70 years) and younger patients (age < 70 years).

**TABLE 3.** End-of-Treatment Reasons With a Frequency ≥ 1% in Older (Age ≥ 70 Years) and Younger Patients (Age < 70 Years)[a]

| End-of-Treatment Reason | Age ≥ 70 y (n = 250) | Age < 70 y (n = 1016) | P[b] |
|---|---|---|---|
| Treatment completed | 46% (n = 115) | 54% (n = 551) | .02 |
| Adverse event | 14% (n = 36) | 9% (n = 96) | .02 |
| Disease progression | 13% (n = 32) | 18% (n = 186) | .04 |
| Patient refused further treatment | 10% (n = 26) | 5% (n = 52) | <.01 |
| Died during treatment | 11% (n = 28) | 4% (n = 40) | <.01 |
| Other | 5% (n = 13) | 8% (n = 81) | .13 |

[a]Data were missing for 37 patients.
[b]Chi-square tests were used for *P* values except for no response to treatment, development of other disease, and treatment never started, for which Fisher's exact test was used.

were examined, elderly patients experienced less nausea (69% vs 77%; $P < .01$) and esophagitis (50% vs 63%; $P < .01$; Supporting Table 3).

Elderly patients, compared with younger patients, completed treatment less often ($P = .02$), discontinued treatment because of adverse events more frequently ($P = .02$), refused further treatment more frequently ($P < .01$), and died during treatment more frequently ($P < .01$; Table 3). Elderly patients, compared with younger patients, stopped therapy because of disease progression significantly less often ($P = .04$). Data on the study team's attributions of causes of death were available for 729 patients, and deaths attributed to treatment occurred in 6% of elderly patients and 4% of younger patients ($P = .22$).

In the exploratory analysis using the age cutoff of 65 years, patients 65 years old or older (n = 540), compared with patients younger than 65 years (n = 763), had worse OS in the multivariate analysis ($P < .01$) and worse PFS in the multivariate analysis ($P = .01$). The median OS durations for patients 65 years old or older and patients younger than 65 years were 24.6 and 19.3 months, respectively (Supporting Fig. 2). In an exploratory analysis used to investigate the potential contribution of younger patients (defined as patients younger than 50 years), we investigated the OS of patients younger than 50 years (n = 146), patients 50 years old or older but younger than 70 years (n = 903), and patients 70 years old or older (n = 254). Patients younger than 50 years, compared with patients 50 years old or older but younger than 70 years, had better OS ($P < .01$), and patients 70 years old or older, compared with patients 50 years old or older but younger than 70 years, had worse OS ($P < .01$). The median OS durations observed for patients in the age groups of <50, ≥50 to <70, and ≥70 years were 27.2, 23.0, and 17.8 months, respectively (Supporting Fig. 3). In an exploratory analysis of OS for patients enrolled in recent trials versus later trials, patients enrolled in trials with the first patient enrolled before January 1, 1996 (n = 602), were compared with patients enrolled in trials with the first patient enrolled after January 1, 1996 (n = 701). A difference in OS between recent and later trials was not observed ($P = .13$).

## DISCUSSION

Previous studies comparing elderly and younger patients have revealed contradictory OS results. The larger sample size of our study provided a more definitive analysis of OS and a better estimate of the median OS in each of the age subgroups, which will assist future analyses. A retrospective study of 2 randomized trials performed by the National Cancer Institute of Canada revealed similar OS in patients younger than 70 years and patients 70 years old or older (n = 608).[11] In a retrospective study of patients enrolled in a trial of once or twice daily radiotherapy starting with the third cycle, elderly and younger patients experienced similar OS.[10] A retrospective analysis of a phase 3 trial of cisplatin/etoposide with once or twice daily radiation used the age cutoff of 70 years (n = 381) and revealed a statistically significantly worse 5-year OS rate.[9] A previous retrospective study of 3 trials investigating high-dose thoracic radiation revealed that a younger age (<60 years) was independently associated with improved OS in a multivariate analysis (n = 200).[8] Heterogeneity in the patient population and the treatments investigated as well as the smaller sample size may have contributed to the discrepant results from previous studies. Elderly patients experienced worse PFS, and this suggested that disease progression contributed to the worse OS. The difficulty in tolerating and completing chemoradiotherapy probably contributed to the worse PFS. We do not have data on the rate of subsequent therapies, and this may have differed between the elderly and younger patients and may have been a contributing factor to the worse OS as well.

One challenge in performing analyses based on age is selecting the optimal age cutoff. We used the age cutoff of ≥70 years in this analysis to ease comparisons with previous studies in SCLC and non–small cell lung cancer.[9–11,29–31] However, the use of this age is arbitrary and is not based on physiological data or clinical evidence.

Our exploratory analyses revealed similar results for PFS and OS with the age cutoff of 65 years and differences in OS when patients were divided into the following age groups: <50, ≥50 to <70, and ≥70 years. Younger patients may have tolerated therapy better, had fewer comorbidities, or received subsequent therapies at a higher rate, and this may have contributed to the differences in OS. A previous retrospective analysis of LS-SCLC revealed that an age > 70 years was not associated with a higher frequency of radiation therapy interruption.[32] However, patients 50 years old or younger, compared with patients older than 50 years, were less likely to have treatment interruptions, but an association with radiation treatment interruptions and OS was not observed. Additional studies will assist in elucidating the treatment compliance and tolerability of therapy in young and elderly patients with LS-SCLC.

Nine of the 11 trials used cisplatin-based chemotherapy, which contributed to the adverse events observed. Importantly, half of the patients received platinum-based therapy in combination with a novel agent, which may have contributed to the rate of adverse events observed. Elderly patients may have been more susceptible to the adverse events associated with the investigational agent because of differences in drug clearance or due to drug-drug interactions because of more concurrent medications.

There have been improvements in the antiemetics used with cisplatin- and carboplatin-based therapies since these trials were performed, which would have reduced the rate of nausea or vomiting in both groups.

We report the frequency of specific adverse events, but we do not have data on the number of cycles of chemotherapy or dose adjustments, and we cannot calculate the rate of adverse events per chemotherapy cycle or chemotherapy delivery. For example, the lower rate of grade 3 or higher vomiting observed in elderly patients may have been due to a lower frequency of vomiting, more frequent dose reductions, or fewer cycles of chemotherapy in the elderly patients. Elderly patients also experienced a lower frequency of grade 3 or higher esophagitis/dysphagia, and we do not have data available to determine whether this was due to more radiation treatment interruptions or patients' not completing the intended radiation therapy. Elderly patients reported a higher rate of grade 3 or higher dyspnea (defined as dyspnea with activities of daily living) but similar rates of radiation pneumonitis and anemia, which can cause dyspnea. It is possible that elderly patients had less pulmonary reserve or more underlying cardiovascular disease and were more likely to develop symptomatic dyspnea with lower grade anemia or radiation pneumonitis. The assessment of adverse events is complex because a combination of underlying comorbidities, treatment-related adverse events, disease status, and investigator interpretation contributes to attribution and grade.

The higher rate of grade 5 adverse events is concerning. Grade 5 adverse events include deaths from all causes. Elderly patients may have had a higher prevalence of comorbidities, and these may have been responsible for or contributed to their death while they were receiving study therapy. To better assess the cause of the higher rate of grade 5 adverse events in elderly patients, we investigated the attribution according to the study team's assessment, and data were available from 7 studies for 729 patients. Deaths were attributed to the study therapy for 6% of elderly patients and 4% of younger patients ($P$ = .22). The smaller sample size limits our interpretation, and attributing causality is difficult; this analysis should be interpreted cautiously.

One hazard of using clinical trial data is that the patient population enrolled in clinical trials may differ substantially from patients seen in routine clinical practice. The eligibility criteria, especially organ function, comorbidities, and a history of prior malignancy, restrict the elderly patients who can enroll in clinical trials.[33] The median age for patients with SCLC in a recent cohort study was 69 years, but the median age in a recent trial of chemoradiotherapy for LS-SCLC was approximately 62 years.[4,7] The use of cisplatin and physician practice patterns may have limited the enrollment of elderly patients to the "fit" elderly or the patients perceived as the "fit" elderly. However, physicians may have been more lenient in enrolling younger patients with comorbidities and a poor performance status; this was observed in advanced-stage non–small cell lung cancer.[34] Without a more in-depth prospective assessment of patients, such as a comprehensive geriatric assessment, it is difficult to detect the variation in comorbidities in younger and older patients enrolled in studies.[35]

This analysis has weaknesses. The retrospective design of this pooled analysis may have introduced uncontrolled biases. PCI was included in the treatment plan at the discretion of the treating physician in all of the trials. However, we were unable to determine whether individual patients or patients in specific trials received PCI or whether the rate differed between the elderly and younger patients. Thus, we are unable to determine whether PCI contributed to the difference in PFS or OS or to perform subset analyses. The adverse events were recorded over the entire treatment, so we cannot determine whether the chemotherapy alone or

the concurrent chemoradiotherapy portion of the treatment contributed to the differences in the severe adverse events. Patients enrolled in the trials over an extended period, and the characteristics of the elderly patients studied in this analysis may differ from those of the current elderly patient population with LS-SCLC. Another issue is that we did not identify a specific adverse event, such as febrile neutropenia, that is easy to address to reduce fatal adverse events. The staging workup has changed, and there is greater use of positron emission tomography/computed tomography staging. These studies also lack central confirmation of the diagnosis of SCLC.

Despite the difficulty in tolerating the therapy, the median OS among elderly patients was 17.8 months, and a significant percentage experienced long-term survival. Appropriate elderly patients should be offered chemoradiotherapy, but this indicates the need for a better assessment of elderly patients. The decision to pursue chemoradiotherapy should include patient preferences and a discussion about the benefits and risks associated with the therapy. A comprehensive geriatric assessment is a method of assessing vulnerabilities and identifying patients who are more likely to experience chemotherapy adverse events, and it may facilitate a conversation about the risks and benefits of therapy.[35–37] Elderly patients frequently have comorbidities that necessitate concurrent medications, and these can exacerbate adverse events (eg, an antihypertensive medication may exacerbate dehydration or contribute to episodes of hypotension). We recommend a careful review of concurrent medications before therapy is started.

For patients who do not meet the common eligibility criteria for chemoradiotherapy because of organ dysfunction, performance status, or comorbidities, the use of sequential chemotherapy and radiation can be considered. Radiotherapy techniques associated with lower exposure of critical normal tissues (the heart, lungs, esophagus, and immune system) would be desirable for elderly patients.[38,39] The substitution of carboplatin for cisplatin is an option for patients who have contraindications to cisplatin.

Future LS-SCLC trials should prospectively assess the vulnerability of elderly patients to adverse events, incorporate novel methods of monitoring adverse events through patient-reported outcomes, and investigate novel radiation treatments or systemic therapies.[36,40] A phase 3 trial of carboplatin and etoposide alone or with atezolizumab in extensive-stage SCLC revealed an improvement in OS.[41] Recently, the US Food and Drug Administration approved single-agent nivolumab for patients with extensive-stage SCLC with disease progression after platinum-based therapy and at least 1 other therapy.[42] Immunotherapy alone and in combination with chemotherapy has the potential to improve efficacy and may lead to fewer severe adverse events than the chemotherapy combinations investigated in these trials. Future trials could prospectively investigate reduced-dose chemotherapy with immunotherapy in elderly patients to improve the tolerability.

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## CONFLICT OF INTEREST DISCLOSURES

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## AUTHOR CONTRIBUTIONS

**Thomas E. Stinchcombe:** Conceptualization, data curation, funding acquisition, project administration, writing–original draft, and writing–review and editing. **Wen Fan:** Data curation, formal analysis, project administration, resources, software, validation, writing–original draft, and writing–review and editing. **Steven E. Schild:** Data curation, formal analysis, investigation, methodology, resources, software, writing–original draft, and writing–review and editing. **Everett E. Vokes:** Data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Jeff Bogart:** Data curation, formal analysis, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Quynh-Thu Le:** Data curation, formal analysis, investigation, methodology, validation writing–original draft, and writing–review and editing. **Charles R. Thomas, Jr:** Data curation, formal analysis, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Martin J. Edelman:** Data curation, formal analysis, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Leora Horn:** Data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Ritsuko Komaki:** Data curation, formal analysis, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Harvey J. Cohen:** Data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing–original draft, and writing–review and editing. **Apar Kishor Ganti:** Data curation, formal analysis, funding acquisition, investigation, validation, writing–original draft, and writing–review and editing. **Herbert Pang:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Xiaofei Wang:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing.

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