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Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database☆

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ABSTRACT

We used the Surveillance, Epidemiology, and End Results (SEER) database to examine the outcomes of patients with limited stage small cell lung cancer (LS-SCLC) over time and to determine if any trends were present with respect to the publication of significant clinical trials. We assembled a cohort of 6271 patients aged 21 years and older with LS-SCLC diagnosed from 1983 to 1998 and followed through 2005. Potential covariates included patient age at diagnosis, sex, race, year of diagnosis, laterality, tumor size, and location (upper lobe, middle lobe, lower lobe, or main bronchus). In multivariate analysis, older age, male sex, African American race, and main bronchus location were all associated with a statistically significant increase in the mortality hazard. When compared to patients diagnosed in 1983–1987 who did not receive radiotherapy, the hazard for mortality was significantly reduced for patients diagnosed in 1988–1992 regardless of whether they received radiotherapy (HR = 0.59; CI 0.52–0.65; $p < 0.0001$) or not (HR = 0.67; CI 0.60–0.75; $p < 0.0001$). Patients who were diagnosed in 1993–1998 and received radiotherapy had similarly improved survival (HR = 0.53; CI 0.47–0.58; $p < 0.0001$), which was better than patients from the same time era who did not receive radiotherapy (HR = 0.77; CI 0.69–0.85; $p < 0.0001$). In conclusion, the survival for patients with LS-SCLC has improved over time. Many factors are likely involved, however we believe that part of this improvement was the result of clinical trials which investigated and subsequently defined chemoradiotherapy as the standard of care. In order to continue to improve clinical outcomes, clinical trials investigating new treatment paradigms are needed.

1. Introduction

Twenty-five years ago clinicians and researchers were poised to make major advancements in the treatment of small cell lung cancer (SCLC). They had devised a unique staging system, established the effectiveness of multiple chemotherapeutic agents and radiation therapy, and even discovered the central nervous system sanctuary which required distinct treatment. Small cell lung cancer was being added to some lists of "curable cancers" [1]. Unfortunately, a recent analysis suggests that only modest improvements in survival have occurred since [2]. It should also be noted that over the past two decades the pace of investigation of treatments for SCLC has stalled. This is reflected by the declining number of SCLC abstracts submitted to the American Society of Clinical Oncology over the past 25 years [3]. The current slow pace of small cell lung cancer investigation is unfortunate as the estimated deaths from this disease are approximately 4% of all cancer mortality [4].

The initial breakthough in small cell lung cancer treatment occurred in the late 1960s with the recognition that small cell lung cancers were more responsive to available chemotherapeu-

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tic agents than an inert compound [5]. While encouraging results were achieved with chemoradiotherapy [6], the standard of care for limited stage (LS) SCLC was chemotherapy alone during the 1970s and early 1980s. As a result, the 1980s saw a flurry of clinical trials investigating chemoradiotherapy vs. chemotherapy alone in LS-SCLC. The publication of Cancer and Leukemia Group B (CALGB) trial 8083 [7] in the New England Journal of Medicine in 1987 showed a benefit in local control, failure-free survival, and overall survival with the addition of thoracic radiation combined with doxorubicin-based chemotherapy for patients with LS-SCLC. This trial initiated a shift in the standard of care for patients with LS-SCLC. Subsequently, two meta-analyses [8,9] published in late 1992 comprising, 14 total trials, confirmed the benefit of thoracic radiotherapy by demonstrating a survival benefit of 5.4% for chemoradiotherapy over chemotherapy alone in the treatment of LS-SCLC. CALGB 8083 utilized doxorubicin-based chemotherapy; cisplatin plus etoposide was originally shown to be equivalent to doxorubicin-based chemotherapy in patients with extensive stage SCLC [10]. These results were extrapolated for the use in LS-SCLC without confirmation because of the compatibility with radiotherapy and a significantly better toxicity profile. Subsequent clinical trials did confirm the superiority of cisplatin–etoposide–radiotherapy regimen [11].

To determine if any trends exist in the outcomes of patients with LS-SCLC in the community, we used the Surveillance, Epidemiology, and End Results (SEER) database to examine survival after radiotherapy among this population. We hypothesized that clinical trials have impacted outcomes positively and this initiated the diffusion of definitive radiotherapy into the patterns of practice.

2. Methods

Data for this retrospective study was obtained from the National Cancer Institute's SEER program using the 17-Registry 1973–2003 data set, November 2005 Submission, released May 2006. The SEER Program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis, first course of treatment, and patient survival data.

From the SEER database, we assembled a cohort of patients aged 21 years and older with pathologically confirmed, non-metastatic small cell lung cancer diagnosed from 1983 to 1998 and followed through 2005. To focus on selecting patients with LS-SCLC, we restricted the study to patients with no adenopathy, ipsilateral hilar adenopathy, ipsilateral mediastinal adenopathy, or regional adenopathy (NOS). Patients were excluded if they were specifically coded as having contralateral mediastinal, contralateral hilar, and supraclavicular adenopathy. Histologic codes 8041–8045 were designated as small cell lung cancer. Patients who received radiotherapy were compared to patients who did not receive radiotherapy. Potential covariates included patient age at diagnosis, sex, race, year of diagnosis, laterality (right vs. left), tumor size, and location (upper lobe, middle lobe, lower lobe, or main bronchus). Data on performance status, use of adjuvant chemotherapy, and thoracic radiotherapy treatment details (dose, fractionation, beam energy, field size, etc.) were not available within the SEER database and are not included in this analysis.

3. Statistical analysis

The chi-square test was used to compare the prevalence of covariates among patients who did and did not receive radiotherapy. Radiotherapy utilization was defined by the ratio (# of patients receiving radiotherapy)/(# of patients not receiving radiotherapy) for each year based on age (<60 years old, 60–69 years old, and ≥70 years old). These results were plotted for each year and fit with a first-order linear regression. Proportional hazards models were used to examine the adjusted association of radiotherapy and potential covariates with overall survival. Hazard ratios greater then 1.00 were associated with worse survival.

Patients contributed person-time from the date of their diagnosis until they died. To address our hypothesis that the publication of significant clinical trials led to changes in practice we assigned patients to one of six groups defined by the combination of having radiotherapy or not and time period of treatment (1983–1987, 1988–1992, and 1993–1998). We chose to stratify the year of diagnosis at 1987, as that was the year CALGB 8083 was published [7]. We chose to stratify at the second time point, 1992–1993, since that was the time of publication of two meta-analysis investigating radiotherapy in limited stage SCLC [8,9]. Adjusted models also included patient age at diagnosis, sex, race, laterality, and location. Preliminary analyses demonstrated a non-linear relationship between age and 5-year survival. As a result, we elected to categorize age for the purposes of modeling to accommodate the non-linearity. The impact of age on survival was further studied by both examining interactions terms between radiotherapy use and patient age and investigating subset analysis for mortality based on age.

All data were analyzed using SAS Version 8.02 (SAS Institute, Cary, NC) statistical software package. This study was performed after being approved by the Wake Forest University Health Sciences Institutional Review Board and is in full compliance with federal, state, and institutional regulations and guidelines.

4. Results

This analysis included 6271 patients; 3425 (55%) received radiotherapy while, 3846 (45%) did not receive radiotherapy. The median patient age at diagnosis within the cohort was 67 years (range = 27–97 years). The median follow-up for all patients was 1.2 years. Younger patients, non-Caucasian patients, patients with larger tumors, and patients with primaries located in the upper lobe or at the main bronchus had a higher frequency of radiotherapy use; females were more likely to receive radiotherapy than males, although the difference was small. Radiotherapy use did not differ significantly with respect to laterality (Table 1).

As shown in Fig. 1, the proportion of patients with LS-SCLC over 70 years old has increased such that by 1993–1998, they accounted for almost half of the cohort. As shown in Fig. 2, patients under the age of 60 and between the ages 60–69 both showed an increase in radiotherapy utilization, with a greater increase for the younger

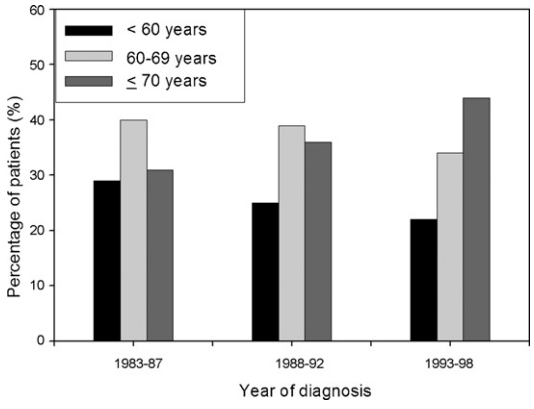

Fig. 1. Distribution of patients with LS-SCLC by age for different time periods.

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Table 1
Characteristics of patients with LS-SCLC

	Radiotherapy (%) ($N = 3425$)	No radiotherapy (%) ($N = 2846$)	p
Age			
<50 years	235 (70%)	99 (30%)	<0.0001
50–59 years	769 (64%)	437 (36%)	
60–69 years	1332 (58%)	977 (42%)	
70 and over	1089 (45%)	1333 (55%)	
Gender			
Male	1863 (56%)	1466 (44%)	0.0277
Female	1562 (53%)	1380 (47%)	
Race			
White	2953 (54%)	2516 (46%)	0.0344
African American	288 (59%)	198 (41%)	
Other	184 (58%)	132 (42%)	
Laterality			
Right	1962 (55%)	1586 (45%)	0.2154
Left	1463 (53%)	1369 (46%)	
Size			
<3 cm	1477 (51%)	1432 (59%)	<0.0001
3–5 cm	507 (55%)	419 (45%)	
>5 cm	1441 (60%)	995 (41%)	
Subsite			
Main bronchus	409 (57%)	303 (43%)	<0.0001
Upper lobe	2145 (57%)	1619 (43%)	
Middle lobe	191 (48%)	203 (52%)	
Lower lobe	678 (48%)	721 (52%)	
Year of diagnosis			
1983–1987	650 (51%)	629 (49%)	0.0031
1988–1992	869 (54%)	738 (46%)	
1993–1998	1906 (56%)	1479 (44%)	

p value demonstrating significance of frequency difference by χ^2 with respect to radiotherapy use for variables within each patient characteristic.

patients. However, for patients' age 70 and older, no increase in radiotherapy utilization was observed.

On univariate analysis for all patients, male sex and African American race were associated with a decreased 5-year survival. The use of radiotherapy was associated with a significant increase in survival. Lastly, patients diagnosed more recently showed modest, but significant, increases in survival (Table 2).

Multivariate analysis demonstrated that older age, male sex, African American race, and main bronchus location were all associated with an increase in the mortality hazard (Table 3). When compared to patients diagnosed in 1983–1987 who did not receive

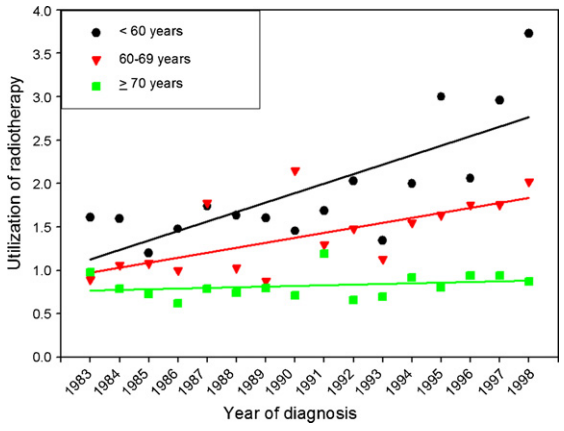

Fig. 2. Change in radiotherapy use for patients with limited stage SCLC with respect to age and year of diagnosis. The black, red and green line represent patients age under 60, age 60–69, and age 70 and older, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Table 2
Univariate analysis of 5-year overall survival for patients with LS-SCLC

	5-year OS (%)	p
Age		
<50 years	15	<0.0001
50–59 years	19	
60–69 years	14	
70 and over	8	
Gender		
Male	11	<0.0001
Female	14	
Race		
White	13	0.0091
African American	8	
Other	10	
Laterality		
Right	12	0.9621
Left	12	
Size		
<3 cm	15	<0.0001
3–5 cm	13	
>5 cm	9	
Subsite		
Main bronchus	11	0.0036
Upper lobe	13	
Middle lobe	15	
Lower lobe	12	
Year of diagnosis		
1983–1987	10	<0.0001
1988–1992	12	
1993–1998	13	
Radiotherapy use		
Yes	13	<0.0001
No	11	

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Table 3
Multivariate analysis of overall survival for patients with LS-SCLC

	HR	CI (95%)	p
Age			
>70	1.66	1.55–1.78	<0.0001
60–69	1.25	1.17–1.34	<0.0001
<60	1.00 (Ref.)		
Gender			
Female	0.91	0.87–0.96	0.0007
Male	1.00 (Ref.)		
Race			
African American	1.19	1.08–1.30	0.0004
Other	1.07	0.95–1.20	0.2821
White	1.00 (Ref.)		
Laterality			
Right	0.99	0.94–1.05	0.8301
Left	1.00 (Ref.)		
Size			
<3 cm	0.60	0.55–0.64	<0.0001
3–5 cm	0.76	0.70–0.83	<0.0001
>5 cm	1.00 (Ref.)		
Subsite			
Main bronchus	1.12	1.02–1.24	0.0153
Upper lobe	0.99	0.93–1.06	0.7942
Middle lobe	0.97	0.86–1.09	0.5534
Lower lobe	1.00 (Ref.)		
Radiotherapy use by year of diagnosis			
No radiotherapy			
1983–1987	1.00 (Ref.)		
1988–1992	0.67	0.60–0.75	<0.0001
1993–1998	0.77	0.69–0.85	<0.0001
Radiotherapy			
1983–1987	1.03	0.93–1.12	0.5719
1988–1992	0.59	0.52–0.65	<0.0001
1993–1998	0.53	0.47–0.58	<0.0001

radiotherapy, the hazard for mortality was significantly reduced for patients diagnosed in 1988–1992 regardless of whether they received radiotherapy (HR = 0.59; CI 0.52–0.65; $p < 0.0001$) or not (HR = 0.67; CI 0.60–0.75; $p < 0.0001$). Patients who were diagnosed in 1993–1998 and received radiotherapy had similarly improved survival (HR = 0.53; CI 0.47–0.58; $p < 0.0001$) which was better than patients from the same time era who did not receive radiotherapy (HR = 0.77; CI 0.69–0.85; $p < 0.0001$). We did perform our analysis including the 534 patients we excluded because they were identified as containing contralateral mediastinal, contralateral hilar, and supraclavicular adenopathy; the results did not differ. Interaction terms were investigated between radiotherapy use and patient age; none reached significance.

In an effort to quantify the impact of radiotherapy use on survival, a multivariate analysis was performed with radiotherapy for each individual year entered as a categorical variable and adjusted for by other potential covariates and compared to all patients not receiving radiotherapy. The results presented in Fig. 3, show that after 1987, the use of radiotherapy was associated with a significant reduction in mortality which was consistent through 1998. We also performed subset analysis based on the patient age (<60 years old, 60–69 years old, and ≥70 years old). The mortality hazard ratio for radiotherapy use appeared consistent in each age group (Fig. 4).

5. Discussion

The survival for patients with LS-SCLC has improved over the last 20 years. The hypothesis we investigated is that this increase in survival is secondary to the adoption of definitive chemoradiotherapy

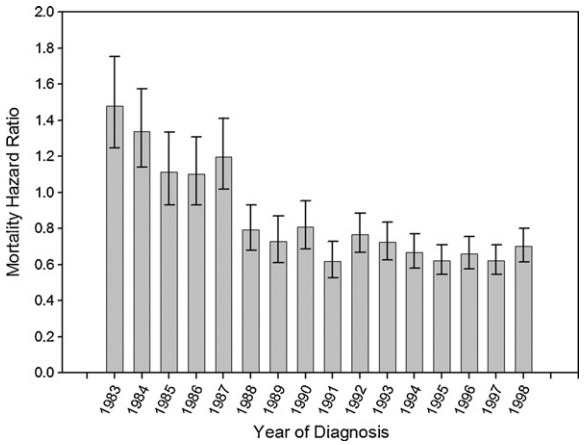

Fig. 3. Proportional hazards multivariate model stratified by radiotherapy use for each year of diagnosis. Hazard ratios (HR) for all-cause mortality (no radiation is the reference group) with 95% confidence intervals.

(over chemotherapy alone) as defined by the results of published multi-institutional clinical trials; however, this is difficult to prove. In our analysis, the positive outcomes appear to correlate with radiotherapy utilization. As a result, we feel our results suggest our hypothesis to be true.

Many other factors are potentially responsible for the improvement in survival we have observed besides clinical trials; these include more effective systemic therapy, improved staging, and better supportive care. We have already discussed improvements in supportive care. Both computed tomography (CT) and magnetic resonance imaging (MRI) of the brain have allowed for better determination of a patient's stage (limited or extensive); this would then dictate an appropriate therapy. Improvements have similarly occurred in the supportive care associated with chemoradiotherapy. Examples would range from the importance of hydration before administering cisplatin-based chemotherapy to the medical management of esophagitis. All are reasonable alternative explanation for our findings. It is difficult to determine the impact these advances, separate of clinical trial, had on our results.

In our analysis, we found that patients diagnosed between 1983 and 1987 had a significantly increased hazard for mortality, regardless of radiotherapy use. We suspect that the publication of CALGB

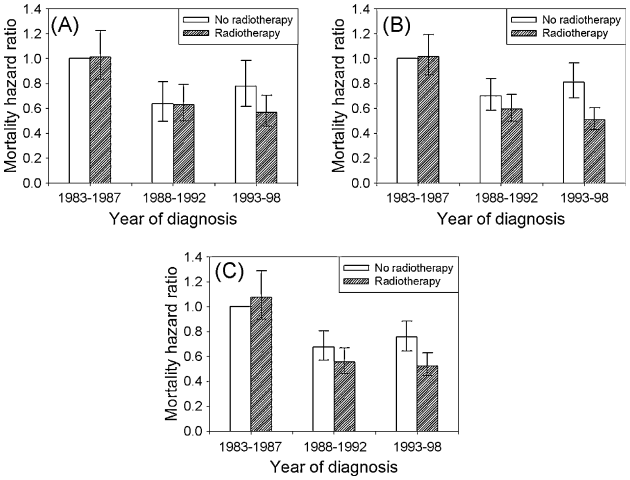

Fig. 4. Proportional hazards multivariate model stratified by radiotherapy use for age-based subsets. Subsets included patients (A) under age 60, (B) age 60–69, and (C) age 70 and over and older. Hazard ratios (HR) for all-cause mortality with 95% confidence intervals.

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8083 in 1987 helped initiate the paradigm shift to chemoradiotherapy that disseminated into the community and became the standard of care. For patients diagnosed 1988–1992, it does appear that overall mortality had decreased when compared with the previous time era. This trend continued with time as the routine use of chemoradiotherapy for LS-SCLC continued to be accepted into general practice. In support of this, we found that patients diagnosed in 1993–1998 treated with radiotherapy have the lowest risk of mortality. While SEER is limited in the information that is available, we feel that changes in mortality related to both radiotherapy use and year of diagnosis provide evidence to support the theory that positive clinical trials have helped to alter the prognosis of LS-SCLC.

The SEER database does not specifically code for SCLC stage. We selected patients with SCLC confined to one hemi-thorax without pleural effusion in our analysis to try and accurately create a dataset of patients with LS-SCLC. This included patients considered to have regional lymph node involvement, but not those considered to have contralateral involvement. Our intent in selecting these patients was to define a cohort of patients whose disease could be encompassed by a tolerable radiation field to meet the requirements of LS-SCLC. We were concerned that if we were not strict in our selection criteria, we risked contaminating our cohort with extensive stage SCLC and thus inflating the importance of radiotherapy. With the integration of CT into the work-up for patients, a contrary opinion exists that our selection criteria might have excluded patients with more advanced disease in the later years examined. Therefore, we performed the analysis both including and excluding the patients with contralateral adenopathy. The results for either analysis did not change.

A major limitation of our investigation is that within the selected cohort, we are unable to predict why or why not radiotherapy was administered. Previous reports have shown that the publication of results from randomized clinical trials can have a dramatic effect on treatment patterns [12–14]. We identified a change in overall survival which appears to be related to more effective radiotherapy. The presentation of prospective data can have significant impact on the patterns of care. Giordano et al. [15] demonstrated that the oral presentation of a single study at a national conference was temporally associated with an increase in the use of taxanes for primary breast cancer, even before study publication or Food and Drug Administration approval. Still, it is likely the treatment prescribed by an oncologist can be influenced by many different factors. Tamoxifen use after surgery for ductal carcinoma in situ increased after presentation of the NSABP B-24 results [16]. Rates varied substantially by institution, suggesting that physicians differ in how they weigh the benefit against the potential adverse effects.

Movsas et al. published the results of a Patterns of Care Study (PCS) investigating the treatment patterns for patients with lung cancer in 1998 [17]. While 42,335 patient records were reviewed, this study included only 72 patients with LS-SCLC. It is important to note in this study that less than 5% of the patients did not receive both radiotherapy and chemotherapy. While we cannot state that every patient within our analysis treated with radiotherapy also received chemotherapy in the later years, our assumption that such is did occur would appear valid. Furthermore, PCS does not report survival analysis which is contained in our analysis of the SEER database. Thus, we consider it important to examine the two results together. Doing such suggests that we (oncologists) have learned from clinical trials, supporting the use of chemoradiotherapy for LS-SCLC to improve outcomes.

Meta-analyses [18–20] investigating the timing of radiotherapy have demonstrated that a short time between the initiation of chemotherapy and the subsequent completion of radiotherapy is prognostic for survival. The SEER database did not provide information on the timing of radiotherapy. We were unable to analyze (1) if the timing of radiotherapy (early vs. late) changed during the time period examined and (2) if this had any impact on our findings. In the CALGB experience, early radiotherapy resulted in a dose reduction that continued throughout the rest of the chemotherapy [7]. Effective chemotherapy shrinks the tumor, reducing toxicity to the lungs and esophagus, and enhancing the therapeutic gain of delayed radiotherapy. Those who advocate early radiotherapy commonly cite the Intergroup trial [21] (where chemotherapy and radiotherapy started on day 1), which demonstrated the best prospective survival data to date. For patients with a good performance status and nonbulky disease, intensive therapy with early radiotherapy is appropriate. For patients with either a poor performance status or very bulky disease, delaying the initiation of radiotherapy until the third cycle of chemotherapy to increase the therapeutic result would seem prudent. As the elderly comprise increasing portions of patients with SCLC, determining which patients will benefit from intensive therapy and which will benefit from delayed radiotherapy becomes critical.

In our analyses, we noted an association between age and both RT use and year of diagnosis. The phase III trials supporting chemoradiotherapy as the superior treatment modality largely excluded or underrepresented patients over the age of 70. Furthermore, one of the meta-analyses suggested that the survival benefit from chemoradiotherapy was restricted to younger patients [8]. Given the toxicity associated with chemoradiotherapy, the question arises which elderly patients are suitable for intensive therapy. Age may in part be a surrogate for other factors that influence therapy intensity such as co-morbidity and performance status. While the percentage of patients over the age of 70 appeared to be increasing with the greatest frequency, the use of radiotherapy for this subset did not. The trends in survival did not appear to be much different whether patients were over the age of 70 or not. As the elderly comprise increasing portions of patients with SCLC, determining which patients will benefit from intensive therapy and which will benefit from delayed radiotherapy becomes critical. Limited available evidence does suggest that abbreviated therapy may still be of benefit to elderly and infirm patients [22].

The most recent phase III cooperative trial for limited stage SCLC was published in 1999 [21]. The results demonstrated that 45 Gy of radiotherapy given via a twice daily (accelerated hyperfractionation) technique was superior to the 45 Gy given with once daily fractionation. Many experts in the field have been critical of accelerated hyperfractionation radiotherapy, citing either unacceptably high toxicity or cumbersome requirements. A recent survey of nearly 700 radiation oncologists showed that only 23% of radiation oncologists used accelerated hyperfractionation in their practice (unpublished data from S. Fong).

It has been nearly 15 years since the last patient was accrued to an U.S. Intergroup phase III trial trying to determine the optimal radiotherapy treatment for this disease. Currently, both CALGB and the Radiation Therapy Oncology Group (RTOG) have initiated a phase II/III trial comparing: (a) 45 Gy given via hyperfractionation; (b) 70 Gy given via standard daily administration and (c) 61.2 Gy given via a concomitant boost technique. Based on our results which suggest that prospective clinical trials can improve outcomes for patients with limited stage SCLC, it is important that this trial be offered to all eligible limited stage SCLC patients.

6. Conclusion

Our results show a significant improvement in survival for patients with limited stage SCLC over the past two decades. We

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believe that this increase in survival was the result of clinical trials which investigated and subsequently defined chemoradiotherapy as the standard of care. In order to improve outcomes for patients with this disease, it is necessary that all eligible patients be offered participation in clinical trials. Such trials need to be designed reflecting the changing age of patients with limited stage SCLC.

Conflict of interest

No actual or potential conflict of interest exists connected to any of authors of this manuscript and its content.

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