

Continued Cigarette Smoking by Patients Receiving Concurrent Chemoradiotherapy for Limited-Stage Small-Cell Lung Cancer Is Associated With Decreased Survival

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Purpose: To determine the impact of continued smoking by patients receiving chemotherapy (CHT) and radiotherapy (RT) for limited-stage small-cell lung cancer (LSCLC) on toxicity and survival.

Patients and Methods: A retrospective review was carried out on 215 patients with LSCLC treated between 1989 and 1999. Treatment consisted of six cycles of alternating cyclophosphamide, doxorubicin, vincristine and etoposide, cisplatin (EP). Thoracic RT was concurrent with EP (cycle 2 or 3) only. Patients were known smokers, with their smoking status recorded at the start of chemoradiotherapy (CHT/RT). RT interruption during concurrent CHT/RT was used as the marker for treatment toxicity.

Results: Of 215 patients, smoking status was recorded for 186 patients (86.5%), with 79 (42%) continuing to smoke and 107 (58%) abstaining during CHT/RT. RT interruptions were recorded in 38 patients (20.5%), with a

median duration of 5 days (range, 1 to 18 days). Median survival for former smokers was greater than for continuing smokers (18 v 13.6 months), with 5-year actuarial overall survival of 8.9% versus 4%, respectively (log-rank $P = .0017$). Proportion of noncancer deaths was comparable between the two cohorts. Continuing smokers did not have a greater incidence of toxicity-related treatment breaks ($P = .49$), but those who continued to smoke and also experienced a treatment break had the poorest overall survival (median, 13.4 months; log-rank $P = .0014$).

Conclusion: LSCLC patients who continue to smoke during CHT/RT have poorer survival rates than those who do not. Smoking did not have an impact on the rate of treatment interruptions attributed to toxicity.

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TOBACCO USE causes cancer in humans. A number of reports have also suggested that cancer patients who smoke while receiving treatment for their malignancies have poorer outcomes compared with their nonsmoking counterparts. To date, this association has been most clearly demonstrated by the prospective study of Browman et al,¹ which showed that patients with stage III/IV head and neck cancer who continue to smoke during radiotherapy have lower rates of response and decreased survival compared with patients who do not smoke while receiving treatment. Retrospective series of patients with renal,² bladder,³ and especially glottic cancers⁴⁻⁶ also indicate a link between smoking during treatment and decreased efficacy of cancer therapies.

Previous work on the relationship between smoking and limited-stage small-cell lung cancer (LSCLC) had shown that smoking cessation after successful treatment of the disease is associated with fewer smoking-related second primary cancers.⁷

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The impact of continued smoking during treatment on outcomes for LSCLC patients is less defined. A search of the medical literature reveals only two reports from the 1980s that deal with the effect of smoking on the survival of patients with small-cell lung cancer (SCLC).^{8,9} In these reports, the study populations included a mix of limited- and extensive-stage patients, with the latter predominating. In neither report did the treatment regimens used reflect contemporary standards of combined-modality chemotherapy (CHT) and radiation therapy (RT), which generally involve concurrent administration of platinum-based CHT during RT.¹⁰ Finally, the results were conflicting, with Johnston-Early et al⁸ reporting worse survival with continuation of smoking and Bergman and Sorenson⁹ finding no difference in survival between those who did or did not smoke while receiving treatment.

To determine whether smoking during treatment affects survival and toxicity in LSCLC, we performed a retrospective review (covering a 10-year period) of patients within a single institution who were treated using a concurrent chemoradiotherapy (CHT/RT) regimen modeled after the best arm of a National Cancer Institute of Canada trial.¹¹ Using this database, we examined survival rates of smokers who continued to use cigarettes during treatment compared with those abstaining. Because a previous study had demonstrated that treatment interruptions caused by toxicity decrease the survival and disease control for LSCLC patients,¹² we also examined the impact of smoking on the rate of treatment interruptions brought on by toxicity.

PATIENTS AND METHODS

A retrospective chart review of all patients with SCLC seen at the London Regional Cancer Center, London, Ontario, Canada, between January 1989 and October 1999 revealed 215 patients treated for a diagnosis of LSCLC.

The management of LSCLC was modeled after the early RT arm of the randomized trial of Murray et al¹¹ in which RT was initiated with the second cycle of a six-cycle CHT program.

All patients had a pathologic diagnosis of SCLC. Pretreatment staging consistently included chest x-ray, computed tomography (CT) of the thorax and upper abdomen, and bone scan. Ultrasound of the abdomen, bone marrow biopsy, and CT of the brain were performed according to clinician preference and/or clinical findings. Some patient-related variables currently recognized as having prognostic value, such as serum lactate dehydrogenase, were inconsistently documented over the 10 years. In addition, a given clinician's definition of LSCLC varied, such that 7% (n = 13) of patients had contralateral supraclavicular nodes at presentation, whereas 1.6% (n = 3) had a malignant pleural effusion.

In this analysis, all patients studied had a smoking history and their smoking status was recorded at the initiation of the treatment regimen. (For those patients who were nonsmokers at the start of treatment, the length of their nonsmoking interval was not always recorded).

CHT

CHT consisted of a six-cycle regimen of cyclophosphamide 1,000 mg/m², doxorubicin 50 mg/m² or epirubicin 50 mg/m², and vincristine 2 mg total dose (CAV or CEV, respectively) alternating at intervals of 3 weeks with etoposide 100 mg/m² and cisplatin 25 mg/m² (EP), with both drugs given on 3 consecutive days.¹¹ All agents were administered by intravenous injections or infusion. Drug dosage adjustments were made according to treatment day neutrophil count and serum creatinine level.¹² Drug schedules evolved over the study decade such that 82% of patients received alternating CAV or CEV plus EP and 18% received six cycles of EP.

RT

Two RT prescriptions were used over the period studied. In all cases, patients were treated with high-energy photons (≥ 4 MV). In the early 1990s, RT consisted of 40 Gy in 15 fractions given over 3 weeks in keeping with the trial design of Murray et al.¹¹ A posterior cord shield was used to limit the spinal cord dose to 35 Gy. Treatment fields encompassed all gross tumor, involved regional lymph nodes, and tissues at risk for microscopic disease, with a 2-cm margin. In the later 1990s, after an internal institutional review, total RT dose was modified to 50 Gy in 25 fractions over 5 weeks with CT planning, limiting spinal cord dose to ≤ 45 Gy. This change was made to reflect conventional RT prescribing.¹³ Target definitions and volumes were otherwise the same as for the 40-Gy prescription. RT was administered with the second or third CHT cycle in 85% of patients and always concurrently with EP alone.

Prophylactic cranial irradiation (PCI), consisting of 25 Gy in 10 fractions over 2 weeks, was administered after CHT/RT and after full restaging, which consisted of CT imaging of the head, chest, and abdomen, as well as bone scanning. It was offered only to those who demonstrated complete responses to CHT and thoracic RT and according to individual clinician preference.

Treatment Interruptions

Hematologic criteria for interruptions during concurrent CHT/RT included absolute neutrophil count $\leq 1,000$ /mL, neutropenic fever or sepsis, and thrombocytes $\leq 80,000$ /mL. Locoregional criteria included severe esophagitis (ie, severe odynophagia/dysphagia and intolerable pain), impaired nutrition with nausea or vomiting, and dehydration requiring hospitalization. For the purpose of this study, the marker for any toxicity-related treatment break was measured by the length (in days) of the interruption in the RT schedule arising during the concurrent phase of LSCLC treatment.

Analysis

Overall survival was defined as the interval between the date of pathologic diagnosis and death or last follow-up, with any death being defined as an event. Disease-specific survival was defined as the interval between the date of pathologic diagnosis and the date of first recurrence or last follow-up, with recurrences treated as events. Survival estimates were obtained using Kaplan-Meier methodology. Cox regression was used to test the impact of multiple variables on overall and disease-free survival.

RESULTS

Of the 215 LSCLC patients treated, 126 were men (58.6%) and 89 were women (48.4%). Median age at diagnosis was 63 years (range, 32 to 94 years). Median Karnofsky performance status for the entire study cohort was 80 (range, 60 to 90). At the time of analysis, 23 patients (10.7%) were alive and 192 were dead (89.3%). Smoking status was recorded for 186 cases (86.5%), with 79 continuing smokers (42%) and 107 not smoking on treatment (58%). Twenty-nine cases lacked sufficient data for analysis. With respect to treatment, 96% achieved the planned RT dose and 90% completed their CHT planned regimen. Interruptions at any CHT cycle were recorded for 39% of patients. Median follow-up interval for the 186 patients was 14.8 months (range, 2.3 to 84.5 months).

The patients were analyzed using a range of selected characteristics and prognostic factors to determine whether patients still smoking while receiving treatment were comparable to those not smoking. These results are listed in Table 1. Other than a higher proportion of women who continued to smoke compared with men, there were no significant imbalances in patient and treatment characteristics between the two groups.

Thirty-eight (20.5%) of the 186 patients had RT breaks during concurrent CHT/RT because of hematologic and/or locoregional toxicities. Myelosuppression caused the majority of treatment prolongations (88%). The median duration of a treatment break was 5 days (range, 1 to 18 days). Table 2 provides the distribution of toxicity-related treatment breaks as a function of smoking status. There was no significant difference in the number of treatment interruptions between continuing and abstaining smokers ($P = .49$).

Table 1. Comparison of Patient and Treatment Characteristics According to Smoking Status During Chemoradiation

	Smoking		Not Smoking		P
	No. of Patients	%	No. of Patients	%	
Age, years					
< 60	28	35	32	30	.4
≥ 60	51	65	75	70	
Sex					
Male	36	46	76	71	.0005
Female	43	54	31	29	
KPS					
60 to 70	32	41	56	52	.11
80 to 100	47	59	51	47	
Ipsilateral S/C nodes					
Yes	13	16	12	11	.3
No	66	84	95	89	
Pleural effusion					
Yes	1	1	2	2	.7
No	78	99	105	98	
PCI					
Yes	19	24	20	19	.37
No	60	76	87	81	
RT dose					
40 Gy/15 fractions	50	63	67	63	.92
50 Gy/25 fractions	29	37	40	37	
ChT interruption only					
Yes	30	39	42	39	.968
No	47	61	65	61	

Abbreviations: KPS, Karnofsky performance status; S/C, supraclavicular; PCI, prophylactic cranial irradiation; RT, radiation therapy; ChT, chemotherapy.

Table 2. Comparison of Toxicity-Related Treatment Breaks According to Smoking Status During Chemoradiation

	Smoking		Not Smoking		P
	No. of Patients	%	No. of Patients	%	
Treatment break	18	9.7	20	10.8	.49
No treatment break	61	32.8	87	46.7	
Total	79	42.5	107	57.5	

Actuarial overall and disease-free survival curves according to smoking status are presented in Figs 1 and 2. There was a significant difference in actuarial overall survival favoring the nonsmoking cohort (log-rank $P = .0017$). Although statistical significance was not demonstrated for disease-free survival, there was a late separation of the curves in favor of those who did not continue to smoke. Table 3 lists survival estimates according to smoking status. With respect to causes of death, 71 (94.7%) of 75 deaths in continuing smokers were cancer related, compared with 81 (84.4%) of 96 deaths in nonsmokers ($\chi^2 P = .034$), indicating that the poorer survival among smokers was not attributable to an excess number of deaths from noncancer comorbidities.

We analyzed for associations between smoking status and toxicity-related treatment interruptions. As illustrated in Fig 3 and Table 4, survival outcomes were least favorable in patients who continued to smoke and experienced treatment breaks and most favorable in nonsmokers without treatment breaks (log-rank $P = .0014$). To quantify a best outcome achievable for patients receiving treatment as modeled, we determined overall survival values according to PCI delivered, use of treatment breaks, and smoking status (Table 5). Nonsmoking patients who received PCI and had no RT breaks showed a median survival of 23 months and 2-year and 5-year overall survival rates of 50% and 26.8%, respectively.

Sites of first relapse were recorded in 115 patients (62%). Table 6 presents a comparison of sites of first failure according to smoking status. Patients were also stratified by administration of PCI, because it was assumed that early brain relapses could obscure local treatment failure trends. Cranial treatment failure rates reflected PCI use but not smoking status. The proportion of first treatment failures in the chest for patients receiving PCI was

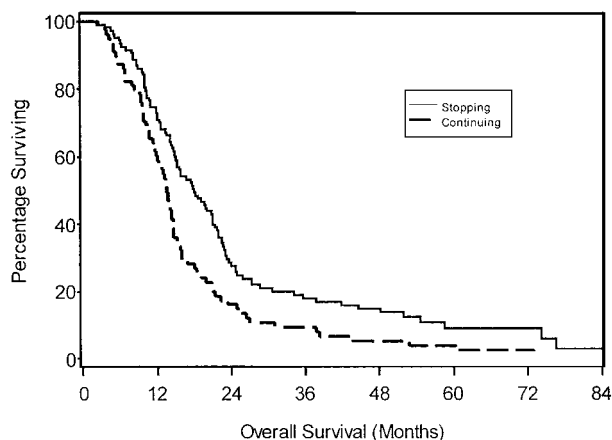


Fig 1. Actuarial overall survival according to smoking status during chemoradiotherapy ($P = .0017$).

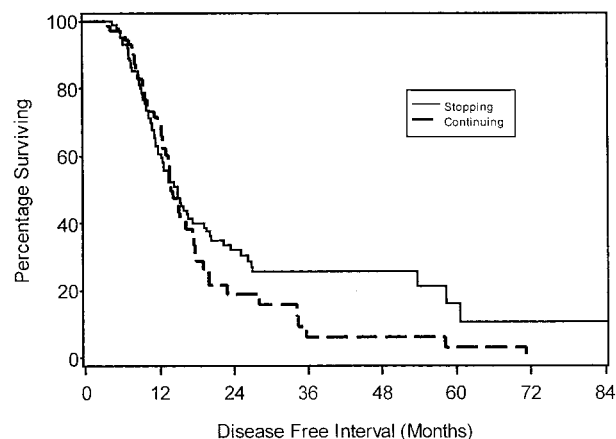


Fig 2. Actuarial disease-free survival according to smoking status during chemoradiotherapy ($P = .21$).

similar between smoking and nonsmoking LSCLC patients, as was the distribution of other nonbrain treatment failures.

A multivariable analysis of prognostic factors including smoking status, sex, age, and volume of limited disease (as per supraclavicular lymph nodes involvement) was applied to overall survival. Continued smoking had the greatest negative impact on survival (hazard ratio = 1.86; 95% confidence interval, 1.34 to 2.57; $P < .001$). Female sex positively influenced survival (hazard ratio = 0.66; 95% confidence interval, 0.48 to 0.92; $P = .014$).

DISCUSSION

Our retrospective review of a 10-year, single-institution experience in managing LSCLC has found that continued tobacco use by smokers during concurrent CHT/RT is associated with decreased survival rates. The strength of the statistical significance of our finding (in view of the relatively small number of analyzable patients) prompted the reporting of this association.

This detrimental effect of smoking while receiving treatment for LSCLC is consistent with results from the prospective study of Browman et al¹ of patients with locally advanced head and neck cancer receiving RT, which showed that continued smoking

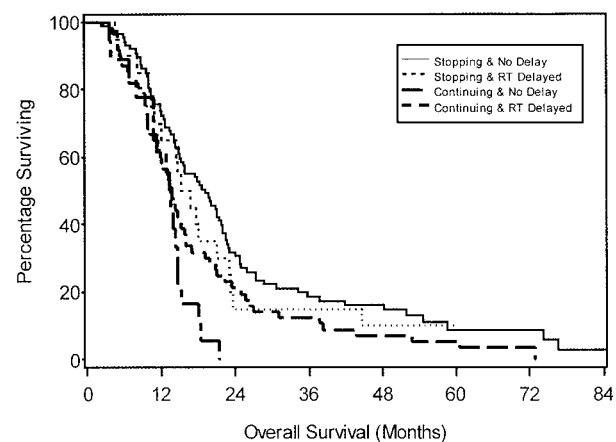


Fig 3. Actuarial overall survival according to smoking status and requirement for toxicity-related treatment breaks (delay) during chemoradiotherapy ($P = .0014$). RT, radiation therapy.

Table 3. Comparison of Survival Outcomes According to Smoking Status During Chemoradiation

	Overall Survival		Disease-Free Survival	
	Not Smoking	Smoking	Not Smoking	Smoking
Median, months	18	13.6	14.8	15.8
2 year, %	28	16	32	18
5 year, %	8.9	4*	18	7

*Log-rank $P = .0017$.

results in lower rates of response and survival compared with those who were nonsmoking. These authors also observed no significant differences in treatment toxicity scores between the persistent and abstaining smokers, paralleling our results of equivalent treatment tolerability (as expressed by the incidence of RT interruptions for toxicity) independent of smoking status. With respect to studies of SCLC, Johnston-Early et al⁸ reported an association between continued smoking and decreased survival. However, their 1980 study was not comparable to our study. Of their 112 patients, 68% had extensive disease. Treatments included four separate CHT regimens, with or without RT or thymosin. They also reported median survivals that were generally inferior to current values, with 47 weeks for ongoing smokers and 70 weeks for those not smoking on treatment. In contrast, a 1988 article by Bergman and Sorenson⁹ stated that smoking during SCLC CHT alone had no impact on survival, with the median survival for former smokers at 39 weeks and persistent smokers at 42 weeks. In this study, 55% of the patients had extensive disease, 35% received a cisplatin-based CHT, and none received RT.

The negative impact of smoking on LSCLC patient survival could not be attributed to an imbalance between the two groups over a range of patient- and treatment-related characteristics examined. Although the type of variables available for analysis was limited by the consistency in data collection over 10 years, of those recorded and analyzed, age, sex, and performance status are recognized as strong predictors of outcome.^{14,15} In that respect, there was the unexpected finding of more women in the persistently smoking population. However, this imbalance was complemented by our study's multivariable analysis that found female sex to have a positive impact on survival after adjusting for smoking and the other prognostic variables. Because others have also shown female sex to be a favorable^{14,15} (or a perhaps neutral¹⁶) prognostic factor in LSCLC, we concluded that the preponderance of women among our study's active smokers would in fact introduce a positive effect on survival that might counterbalance the negative effect of smoking. When we also considered other underlying patient differences that might act as a source of increased mortality from smoking during

Table 4. Comparison of Survival Outcomes According to Smoking Status During Chemoradiation

	No Treatment Break		Treatment Break	
	Not Smoking	Smoking	Not Smoking	Smoking
Median, months	19.1	13.6	15.1	13.4
2 year, %	30.5	21.6	15	0
5 year, %	8.8	5.3	10.0	0

NOTE. Log-rank $P = .0014$.

treatment, we found that the number of cancer deaths was greater for persistent smokers, making it unlikely that persistent cigarette use caused death by exacerbating respiratory or cardiovascular comorbidities.

With respect to treatment tolerance, our toxicity data showed that most interruptions in patient treatment were related to uncomplicated neutropenia. It is now recognized that using such breaks in treatment to palliate the morbidity from concurrent LSCLC CHT/RT can lead to decreased survival and disease control and is not ideal management.¹² However, because toxicity-related RT breaks were actually not found to be more frequent for the continuing smokers in our study, they were likely not the source of the altered survival in persistent tobacco users. That said, it was interesting that the survival curves for subsets of patients stratified by the presence or absence of RT breaks and smoking on treatment demonstrated a synergistic negative impact on survival when both variables were present. This observation was intriguing and indicated that either two different mechanisms were interacting to increase mortality or that one variable was enhancing the negative effect of the other through a common pathway.

As with the survival results, the relapse data from this study also served to generate hypotheses about how smoking compromises treatment efficacy. We found it striking that the proportion of first failures in the chest as well as of distant first failures (accounting for PCI use) was similar for both patient cohorts. By comparison, the study by Videtic et al¹² showed that chest failures were more frequent in patients with treatment breaks, and the study of Browman et al¹ reported loss of local control in patients with head and neck cancer who continue to smoke while receiving RT alone. Both of these reports pointed to loss of RT efficacy as the principal basis for treatment failure and subsequent mortality. Because both distant and local failure in our study seem to be equally promoted by smoking but neither type of failure predominated, smoking may be acting at many levels as it specifically relates to disrupting the response of the small cell to CHT and/or RT. In other words, random competing actions may occur from the various smoke components, so that some components enhance intrinsic cell virulence leading to more

Table 5. Comparison of Survival Outcomes According to Smoking Status, PCI Use, and Treatment Break During Chemoradiation

	PCI				No PCI			
	RT Break		No RT Break		RT Break		No RT Break	
	Smoking	Not Smoking	Smoking	Not Smoking	Smoking	Not Smoking	Smoking	Not Smoking
Median, months	13.4	19	19.9	23.2	12.8	15.6	12.8	17.8
2 year, %	0	16.7	31.3	50	0	14.3	17.4	26.7
5 year, %	0	6.7	0	26.8	0	7.1	7.5	6.5

Abbreviations: PCI, prophylactic cranial irradiation; RT, radiation therapy.

Table 6. Distribution of First Sites of Relapse to Smoking Status and PCI Use

Relapse Site	Smoking					Not Smoking				
	No.	PCI		No PCI		No.	PCI		No PCI	
		No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%
Chest	8	3	37.5	5	62.5	23	8	35	15	85
Brain	27	7	26	20	74	24	0	0	24	100
Bone	4	0	0	4	100	5	1	20	4	80
Liver	4	1	25	3	75	5	0	0	5	100
Other	2	1	50	1	50	3	2	67	1	33
Multiple	4	2	50	2	50	6	1	1	5	83

Abbreviation: PCI, prophylactic cranial irradiation.

effective metastasis and/or resistance, whereas other compounds directly interfere with the cytotoxic actions of CHT and RT.

In this regard, nicotine likely plays a key role in the negative effects of tobacco smoke. SCLC cells highly express a variety and multitude of nicotine-like membrane receptors.¹⁷ Nicotine can then stimulate enhanced proliferation of SCLC cell lines by activating such sites as bombesin-like peptide receptor.¹⁸ In addition, through other receptor subtypes, nicotine promotes the development of autocrine-positive feedback loops through stimulated-release of serotonin¹⁷ or via selective protein kinase activation.¹⁹ The end product of such nicotine exposure is probably a more aggressive small-cell phenotype. Tobacco smoke also contains polyphenolic agents that generate oxidants that may increase tumor invasion and metastasis.²⁰ In SCLC, high levels of oxidative stress have been associated with clinical progression of tumor.²¹ Smoking also increases blood carboxy-hemoglobin,¹ producing relative tissue hypoxia,²² which then impairs the oxygen-dependent workings of RT.^{23,24} Thus therapeutic RT doses have had to be increased to achieve equivalent tumor control in mice acutely exposed to carbon monoxide.²² Smoking also produces impairment in endothelial-related vasodilation that is not subject to the development of nicotine tolerance,²⁵ potentially affecting tissue oxygenation and local delivery of drugs. Lastly, smoking induces changes in natural-killer cell activity and cell-mediated immunity, both of which are linked to accelerated tumor progression.¹

The conclusions of our study are tempered by acknowledgment of the limitations inherent in any retrospective study. We recognize that our data set did not include quantification of cigarette use at the onset of therapy or ongoing verification of patient smoking status during the course of treatment. In our

view, this quantitative information would have been most useful in demonstrating a dose-response effect and would have strengthened the presumed causal relationship between smoking and decreased survival. With respect to corroborating smoking status while receiving treatment, we estimated that any bias this represented would tend toward the underreporting of tobacco use and thus make the present results on the effects of smoking conservative. This view is echoed by Browman et al.¹ We also were unable to collect consistent data on the length of the smoking cessation interval in the patients who were nonsmokers at the start of treatment. That said, it is evident from Browman et al¹ and Johnston-Early et al⁸ that mortality can be influenced by the length of time between smoking cessation and treatment, but that for even short intervals (< 12 weeks), there remains a survival difference between continuing and abstaining smokers, favoring the latter.

We conclude that LSCLC patients who are offered concurrent CHT/RT as definitive management of their disease are at risk if they continue to smoke while receiving treatment. Treating physicians need to ask their patients about their smoking status before initiating treatment and should be prepared to make recommendations regarding means of smoking cessation for the patients to achieve this goal. Prospective assessment of the determinants of continued smoking in this patient population also needs to be carried out so that effective and appropriate interventions can be planned.

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