Importance of Timing for Thoracic Irradiation in the Combined Modality Treatment of Limited-Stage Small-Cell Lung Cancer

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Purpose: **The importance of the timing of thoracic irradiation (TI) in the combined modality therapy of limited-stage small-cell lung cancer (SCLC) was assessed in a randomized trial.**

Methods: **All 308 eligible patients received cyclophosphamide, doxorubicin, and vincristine (CAV) alternating with etoposide and cisplatin (EP) every 3 weeks for three cycles of each chemotherapy regimen. Patients randomized to early TI received 40 Gy in 15 fractions over 3 weeks to the primary site concurrent with the first cycle of EP (week 3), and late TI patients received the same radiation concurrent with the last cycle of EP (week 15). After completion of all chemotherapy and TI, patients without progressive disease received prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks).**

Results: **Although complete remission rates were not significantly different between the two arms, progression-free survival ($P = .036$) and overall survival ($P = .008$) were superior in the early TI arm. Patients in the late TI arm had a higher risk of brain metastases ($P = .006$).**

Conclusion: **The early administration of TI in the combined modality therapy of limited-stage SCLC is superior to late or consolidative TI.**

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ALTHOUGH PATIENTS with unresectable lung cancer have a poor prognosis and are generally treated palliatively, patients with limited-stage small-cell lung cancer (SCLC) constitute a subgroup for whom the intent of therapy is cure. Combination chemotherapy alone yields median survival times of 12 to 16 months and long-term survival rates of 5% to 10%.[1] Because the chest is a common site of recurrence after a chemotherapy-induced remission,[2] combined modality therapy with chemotherapy and thoracic irradiation (TI) seems logical. The superiority of combined modality therapy is supported by promising uncontrolled trials,[3-6] but phase III studies of chemotherapy alone versus chemotherapy plus TI have not always shown benefits for the combined treatment. A number of randomized trials failed to demonstrate a significant survival increase with combined treatment[7-12] and, although others have shown an advantage for the TI-containing arms,[2,13-17] the actual differences were often small and combined modality therapy was associated with more acute and chronic toxicity. Meta-analyses of these studies[18,19] show a small but significant improvement in survival and a major improvement in local control in patients who receive TI therapy. The magnitude of benefit from radiotherapy may be enhanced by more strategic integration with chemotherapy.

The development of drug resistance of mutational origin within tumors is an important factor in determining curability by chemotherapeutic agents.[20] Drug-resistant SCLC is not completely cross-resistant to ionizing radiation.[21] Because the primary tumor is the most heterogeneous portion of the neoplasm, it is the most probable repository of drug-resistant variants and when chemotherapy is commenced, such cells will be unaffected. They will continue to proliferate and metastasize to distant sites. The probability that TI would eliminate chemoresistant tumor should be inversely proportional to elapsed time. Thus, delaying consolidative radiotherapy to the end of chemotherapy should be inferior to the early use of both treatment modalities.

The incidence and severity of toxicity to normal tissue is increased when chemotherapy and radiotherapy are administered concurrently. The risk of pneumonitis, esophagitis, dermatitis, and myelosuppression is determined by the drugs in the chemotherapy regimen and the charac-

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teristics of the irradiation treatment plan. Despite efficacy demonstrated in large cooperative group trials, the administration of chemotherapy combinations that include doxorubicin[2] or lomustine[15] concurrently with TI has not been widely adopted because of treatment-related morbidity and mortality. A pilot study[6] performed at the British Columbia Cancer Agency (1981 to 1983) demonstrated that etoposide and cisplatin (EP) administered concurrently with early TI yielded acceptable toxicity and promising results for limited-stage SCLC. The protocol alternated cyclophosphamide, doxorubicin, and vincristine (CAV) at intervals of 3 weeks with EP for three cycles of each regimen and gave TI with the first cycle of EP (week 3). The median survival was 18 months; 32% survived 2 years and 20% were alive at 5 years. This appeared superior to the 14.5-month median survival, and 22% 2-year and 10% 5-year survival outcomes achieved with consolidative TI administered after six cycles (week 18) of similar chemotherapy in a large Canadian multicenter trial.[22,23]

Based on these theoretical and clinical considerations, the importance of the timing of thoracic irradiation was assessed in a randomized trial by the National Cancer Institute of Canada.

METHODS

Patient Eligibility

All patients with biopsy or cytologically confirmed SCLC were eligible if they were found to have limited-stage disease (defined below), had received no previous radiation therapy or chemotherapy, and had an Eastern Cooperative Oncology Group performance status of 0 (normal activity) to 3 (in bed > 50% of the time, but not bedridden). Patients had to meet standard criteria for renal, hepatic, and hematologic status. Pulmonary function tests were mandatory to determine eligibility. The vital capacity had to be $\geq$ 45% and the forced expiratory volume in 1 second was required to be $\geq$ 40% of the predicted value. Exclusion criteria included age greater than 80 years, serious cardiac disease, and a history of prior malignant tumor unless a disease-free interval of at least 5 years had passed or the tumor was a nonmelanoma skin cancer. Informed consent was obtained from all patients according to the guidelines of the Medical Research Council of Canada and the individual institutional review boards.

Staging Procedures

Each patient underwent the following staging procedures to exclude evidence of metastatic (extensive) disease: chest radiograph, radionuclide bone scanning, brain scan (radionuclide or computed tomography [CT]), liver imaging (radionuclide, ultrasound, or CT scan), bone marrow aspiration and biopsy, and hematologic and biochemical profiles. Patients were considered to have limited-stage disease if detectable cancer was limited to one lung, the mediastinum, and the ipsilateral supraclavicular lymph nodes. Before registration onto the study, a radiation oncologist reviewed the case to determine that all disease could be encompassed according to the radiotherapy guidelines of the study. Patients with pleural effusions were considered to have extensive-stage disease; those with superior vena cava syndrome were eligible if other criteria for limited disease were met.

Diagnostic biopsy or cytologic material was reviewed by a local reference pathologist at each participating center.

Study Design

All patients received the same chemotherapy regimen consisting of cyclophosphamide (1,000 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (2 mg total dose) (CAV) alternating at intervals of 3 weeks with etoposide (100 mg/m^2) and cisplatin (25 mg/m^2), both drugs administered on 3 consecutive days (EP). Each combination was administered for three cycles for a total of six chemotherapy treatments (Fig 1). All agents were administered by intravenous injection or infusion, usually in the outpatient department. Drug dosage adjustments were made according to treatment day and nadir granulocyte counts and treatment day serum creatinine using previously published criteria.[24]

After stratification by center, patients were randomized to early TI given concurrently with the first cycle of EP (week 3) or late TI given concurrently with the last cycle of EP (week 15). The third cycle of chemotherapy (CAV) in the early arm was delayed for 1 week to decrease the interaction of doxorubicin and radiotherapy. Otherwise, the only difference between the early and late arms was a delay of TI for 12 weeks.

TI consisted of 40 Gy in 15 fractions over 3 weeks using cobalt 60 or linear accelerator photons (4 to 25 MeV). No dose corrections were made for lung inhomogeneities. The target volume was based on the prechemotherapy extent of disease and included all gross disease with a 2-cm margin plus the entire mediastinum with a 1-cm margin around uninvolved areas. CT-guided treatment planning was not mandatory. Supraclavicular nodes were treated only if they were initially involved by tumor. Anterior and posterior opposed fields were used throughout to minimize the amount of normal lung irradiated. Posterior cord shielding was used to limit the spinal cord dose to 35 Gy. Co-trimoxazole (one double-strength tablet twice per day) was administered for 21 days from day 1 of the cycle of EP including TI, and radiotherapy was continued regardless of the granulocyte count in the absence of unacceptable toxicity. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was given to patients without progressive disease after completion of chemotherapy and TI. Parallel opposing 20- $\times$ 17-cm fields were used to include the temporal fossae and the intracranial course of cranial nerves. Simulator port films and prechemotherapy chest x-rays were reviewed centrally.

Brain, bone, and liver scans were repeated before prophylactic cranial irradiation, and patients who achieved a complete response (CR) were encouraged to undergo repeat bronchoscopy. Follow-up evaluations including chest radiographs were performed at 6-week intervals for 6 months and every 3 months thereafter. At the time of relapse, scans were repeated as clinically indicated (chest radiographs were routine, but asymptomatic sites were not restaged).

Response Criteria

A CR was defined as the disappearance of all clinical and radiologic evidence of disease, lasting a minimum of 1 month. A partial response (PR) was defined as a decrease of 50% or more in the size of all measurable lesions, lasting at least 1 month. Patients who achieved clinical CR, but who had persistent disease at the time of repeat bronchoscopy, were considered PRs. Stable disease was defined as a less than 50% decrease in size or a less than 25% increase lasting for

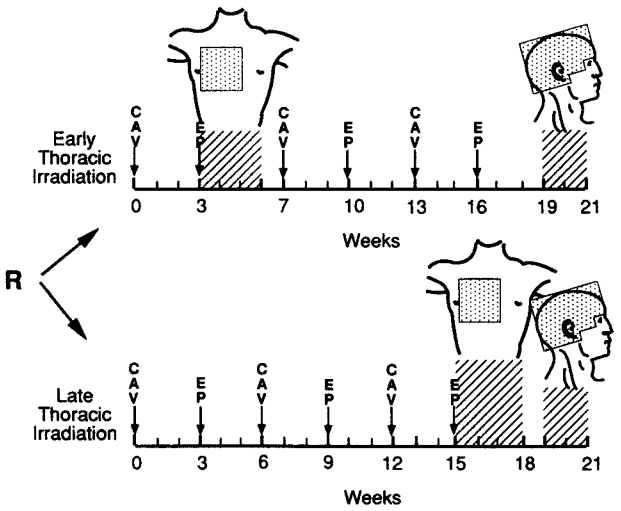

Fig 1. Study schema.

at least 1 month. Disease progression (PD) was defined as an increase of greater than 25% of the cross-sectional area of one or more lesions, or the occurrence of new lesions irrespective of response elsewhere.

Statistical Methods

The trial was designed to provide a power of 80% to detect an improvement in the 2-year survival rate from 20% to 35% at a significance level of .05 (two-sided). Survival time was measured from the beginning of therapy until death or last follow-up, and progression-free survival was measured from the beginning of therapy to the date of disease progression. Progression-free survival and survival were analyzed using the log-rank test[25] and survival curves were estimated by the Kaplan-Meier method.[26] A Cox proportional hazards model[27] was used to adjust for and determine the significance of prognostic variables in the comparison of progression-free survival and overall survival. All levels of significance are two-sided. Significance levels for toxicity comparisons were determined using Fisher's exact test and the linear trends test.

The trial design called for a definitive analysis 2 years after the last patient was enrolled; no interim analyses during accrual were planned.

RESULTS

Patient Population

Three hundred thirty-two patients from 22 Canadian centers were entered onto the study between January 1985 and December 1988. Twenty-four patients (13 assigned to the early arm and 11 assigned to the late arm) were ineligible (7.2%) for the following reasons: extensive-stage disease (n = 5), non–small-cell pathology (n = 10), inadequate pulmonary function tests (n = 3), tumor too large for protocol radiotherapy (n = 4), and disease not assessable (n = 2). Therefore, 308 eligible patients could be analyzed: 155 assigned to the early TI arm and 153 assigned to the late TI arm. Table 1 lists the patient characteristics according to TI timing allocation. No significant differences in prognostic factors were found between the two groups.

Table 1. Characteristics of Eligible Patients by TI Timing Allocation

Characteristic	Early TI (n = 155)	Late TI (n = 153)
Median age, years	61.8	61.6
Sex (%)		
Male	59.4	65.4
Female	40.6	34.6
Performance status (%)*		
0	21.9	22.2
1	65.2	68.0
2	12.3	9.2
3	0.6	0.7
LDH (%)		
Normal	58.7	58.8
Elevated	25.1	25.5
Not done	16.2	15.7
Extent of disease (%)		
Lung only	38.7	39.2
Mediastinum	53.5	56.2
Supraclavicular nodes	7.8	4.6

Abbreviation: LDH, lactic dehydrogenase.

*A score of 0 indicates normal activity: 1, that the patient is ambulatory; 2, that the patient is in bed < 50% of the time; 3, that the patient is in bed > 50% of the time, but not bedridden.

Treatment Delivery

The intended and administered cumulative chemotherapy doses by TI timing allocation are listed in Table 2. Total delivered doses are not significantly different between the two arms. The overall percentages of each agent administered were as follows: cyclophosphamide, 86.7%; doxorubicin, 86.7%; vincristine, 88.9%; etoposide, 86.1%; and cisplatin, 84.0%. The proportion of patients who completed all six chemotherapy treatments was 129 of 155 (83.2%) for the early TI arm and 128 of 153 (83.7) for the late TI arm. The time to administer all chemotherapy in the early TI arm was intended by protocol to be 112 days. The actual mean time for patients who received all cycles was 126 days (SE = 1.3 days). The corresponding times for the late TI arm were 105 days and 118 days (SE = 0.9 days).

Table 2. Total Cumulative Chemotherapy Dose by TI Timing Allocation

	Mean Total Dose (mg/m²)			
	Intended	Early	Late	P
Cyclophosphamide	3,000	2,596	2,598	.46
Doxorubicin	150	129	130	.37
Vincristine	3.6	3.2	3.1	.96
Etoposide	900	772	775	.76
Cisplatin	225	189	187	.87

Table 3. Response to Treatment by TI Timing Allocation

	Percent Response		
	Overall (n = 308)	Early (n = 155)	Late (n = 153)
CR	59.7	63.9	55.6
PR	23.1	20.6	25.5
Stable disease	3.6	5.2	2.0
PD	12.3	9.7	15.0
Inassessable	1.3	0.6	1.9

TI was administered to 149 of 155 (96.1%) patients on the early TI arm and 133 of 153 (86.9%) on the late TI arm. The proportion that received prophylactic cranial irradiation was 133 of 155 (85.8%) for the early arm and 122 of 153 (79.7%) for the late arm. The differences were mainly due to recurrence events, rather than to noncompliance.

Response Rates, Time to Progression, and Survival

The response rates assigned after completion of both chemotherapy and TI are listed in Table 3. Sixty-four percent of early TI patients achieved a CR, compared with 56% of late TI patients. PD during the induction treatment was observed in 9.7% of patients on the early TI arm, as opposed to 15% on the late TI arm. Overall, the response rates were not significantly different between the two arms ($P = .14$).

At the time of the analysis prepared for this publication, minimum follow-up was 32 months and median follow-up was almost 5 years. Kaplan-Meier progression-free survival curves are plotted in Fig 2. The median progression-free survival durations for early and late TI arms are 15.4 and 11.8 months, respectively. Progression-free survival at 3 years was 26% for early TI and 19% for late TI. There was a significant improvement in progression-free survival in favor of the early TI arm both before ($P = .036$ log-rank, .014 Wilcoxon) and after Cox model adjustment for prognostic factors ($P = .047$).

Overall survival was also significantly better in the early TI arm, with a median survival of 21.2 months compared with 16 months for the late arm ($P = .008$ log-rank, .005 Wilcoxon). Survival outcomes by year for early versus late TI were: 2-year, 40% and 33.7%; 3-year, 29.7% and 21.5%; 4-year, 23.7% and 15.1%; and 5-year, 20% and 11% (Fig 3). The survival benefit for the early TI arm remains significant after adjustment for sex and performance status in the final Cox model ($P = .006$).

Forward stepwise Cox regression model was used to assess important prognostic factors. Female sex was a potent prognostic factor for both progression-free survival

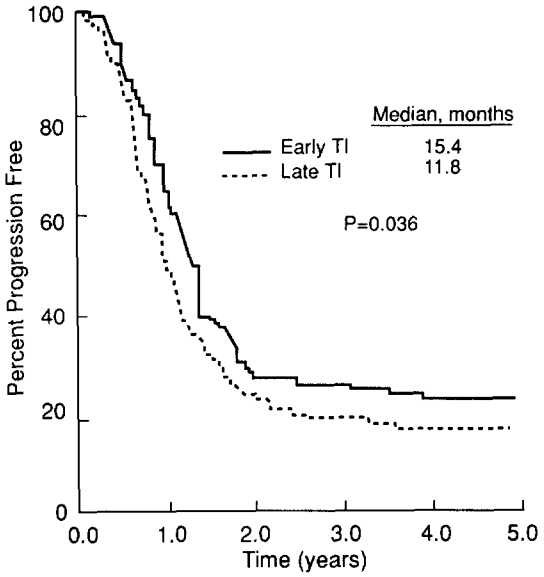

Fig 2. Progression-free survival: early TI v late TI.

($P = .0006$) and survival ($P = .0001$). Performance status was a significant factor for survival only ($P = .015$).

Relapse Pattern

There have been 113 (72.9%) relapses on the early TI arm and 119 (77.8%) on the late TI arm. Local thoracic

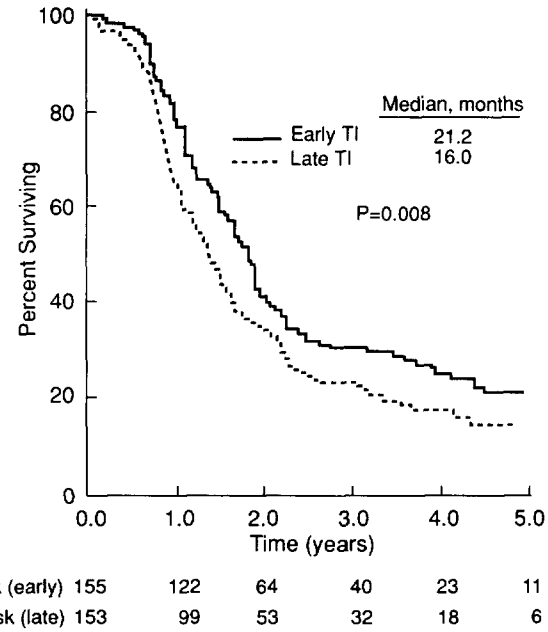

Fig 3. Overall survival: early TI v late TI.

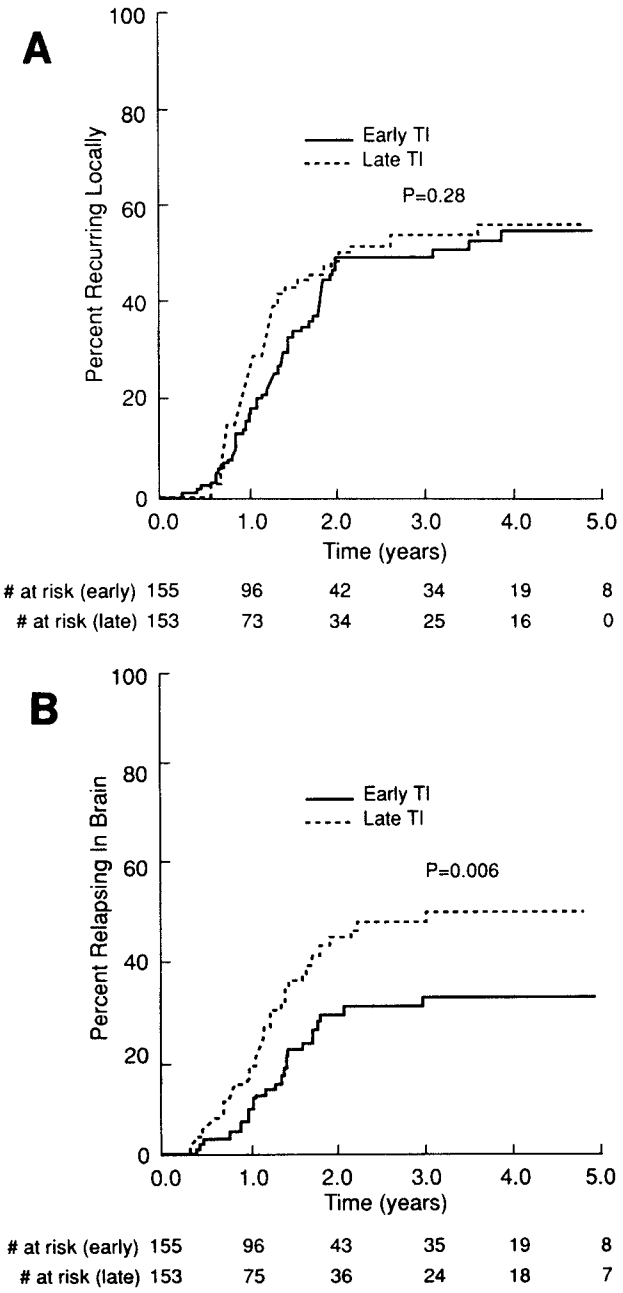

Fig 4. Cumulative plots (A) of the percent of patients recurring locally and (B) of the percent of patients relapsing in brain: early TI v late TI.

recurrence alone was the first site of relapse in 29 of 155 (18.7%) on the early TI arm and 23 of 153 (15.0%) on the late TI arm. Local recurrence plus another site was seen in 18 (11.6%) early TI patients and 22 (14.3%) late TI patients, for a total incidence of first recurrence at the primary site of 30.3% and 29.3%, respectively. A cumulative plot of the risk for local recurrence for all patients is shown in Fig 4A. A trend exists for a higher hazard of local recurrence in the late TI arm (P = .27 log-rank, .12 Wilcoxon). The cumulative risk for local recurrence exceeds 50% in both arms beyond 3 years.

Brain scans were performed both before study entry and before prophylactic cranial irradiation. The latter scan was positive in seven patients (4.5%) on the early TI arm and 14 patients (9.1%) on the late TI arm (P = .12, Fisher's exact test). After prophylactic cranial irradiation, there were 21 (13.5%) recurrences in brain in the early TI arm and 29 (18.9%) in the late TI arm (P = .22). The total proportion of brain metastases in the early arm (28 of 155, 18.1%) was significantly less than in the late TI arm (43 of 153, 28.1%) (P = .042). The proportion of brain-only recurrences was 19 of 28 (67.0%) and 24 of 43 (55.8%) for the early and late TI arms, respectively. A cumulative plot of the probability for brain metastases (Fig 4B) shows a markedly higher risk for patients who received late TI (P = .006 log-rank).

This study did not call for systematic restaging of patients for asymptomatic additional sites of involvement at the time of relapse. A cumulative plot of the probability of systemic metastasis does not show any differences (P = .96).

Toxicity

The incidence of serious toxicity on this phase III trial (Tables 4 and 5) was not different than that anticipated from the pilot study experience.[6] Although severe neutro-

Table 4. Chemotherapy Toxicity by TI Timing Allocation

Type of Toxicity	Percent Response		
	Early (n = 155)	Late (n = 153)	P
Neutropenia, < 0.5 × 10⁹/L	70.3	61.4	NS
Infection			
Neutropenia and fever	4.5	3.3	NS
Septic shock	0.6	0.7	NS
Lethal	0	1.3	NS
Thrombocytopenia, < 25 × 10⁹/L	3.9	2.6	NS
Anemia, < 80 g/L	49	36.8	.03
Cardiac			
Severe	0.6	0.7	NS
Lethal	0.6	0	NS
Renal, Cr > 354 μmol/L	0	0.7	NS
Stomatitis, required IVs	3.9	2.6	NS
Vomiting, required IVs	11.6	15.8	NS
Neurologic			
Severe	0.6	3.3	NS
Life-threatening	0	1.3	NS
Lethal	0.6	0	NS

Abbreviations: NS, not significant; Cr, creatinine; IVs, intravenous fluids.

Table 5. Acute Locoregional Toxicity by TI Timing Allocation

Type of Toxicity	Percent Response		
	Early (n = 149)	Late (n = 133)	P
Pneumonitis	3.2	0.7	NS
Lethal	0	0	
Esophagitis			
None	18.8	24.8	
No diet change	37.6	42.1	
Soft foods	28.8	25.5	.05*
Fluids only	11.4	6.8	
IV fluids	3.4	0.8	
Dermatitis			
Severe	2.0	1.5	
Blisters	4.0	0.7	.02*

Abbreviation: IV, intravenous.

*Linear trend test.

penia was common, infections requiring hospitalization occurred in less than 5% of patients. There were only two treatment-related deaths (1.3%) on each arm. The only types of toxicity that were significantly different and more severe on the early compared with the late TI arms were anemia (< 80 g/L), esophagitis, and dermatitis. Severe lung toxicity was infrequent on this trial.

DISCUSSION

The somatic mutation theory of drug resistance[28] can be used as a conceptual model to divide limited-stage SCLC patients into three groups according to the presence or absence of drug-resistant tumor and its location. For the first group (Fig 5A), mutation to chemotherapy resistance has not occurred, and although the vast majority of patients harbor subclinical metastases outside the chest, all disease is chemosensitive. These patients may be cured with chemotherapy alone provided treatment is given with sufficient dose intensity and total cumulative dose and disease does not persist in a pharmacologic sanctuary site. Unfortunately, only about 5% to 10% of the limited SCLC patient population may be in this category. Thoracic radiotherapy should not be required for these patients, but it could be of benefit if the chemotherapy prescription was inadequate and persistent disease was still localized. The second group (Fig 5B) is of crucial importance to this trial. It includes patients who have chemotherapy-resistant tumor confined to the principal repository of tumor stem cells at the primary site. The early administration of TI may eradicate these clones before they spread outside a reasonable treatment volume and additional chemotherapy can control remaining local and distant chemosensitive tumor. The early reduction in the tumor stem-cell population by definitive local therapy may also decrease the probability that chemoresistant or radioresistant tumor will evolve during treatment. The majority of limited SCLC patients fall into the third group (Fig 5C), where not only has mutation to chemoresistance occurred, but these phenotypes have also disseminated to distant sites. Thoracic radiotherapy may improve the rate of local control, but it cannot change the fatal outcome for all of these patients.

The results of this randomized phase III study are consistent with this model. Although the 12-week delay between the arms in the timing of TI is a small portion of the natural history of this cancer, it clearly has a significant impact on outcome even if the radiographic assessment of chemotherapy efficacy during this period is satisfactory. The effect was not seen in the response to combined modality treatment, as the CR rate in the early TI arm was 63.9% compared with 55.6% in the late TI arm ($P = .14$).

Progression-free survival differences (Fig 2) were significant ($P = .036$), with median of 15.4 months in the early TI arm and 11.8 months in the late TI arm. Three-year progression-free survival rates were 26% and 19%, respectively. Overall survival (Fig 3) was better in the early TI arm, with a median of 21 months versus 16 months in the late TI arm ($P = .008$). More importantly, the probability of long-term survival and cure was enhanced with early TI, with 3- and 5-year survival rates of 29.7% and 20% as opposed to 21.5% and 11% with late TI.

The analysis of the relapse pattern for this study showed a highly significant increase in the probability of brain metastases if local therapy was given late (Fig 4B). The

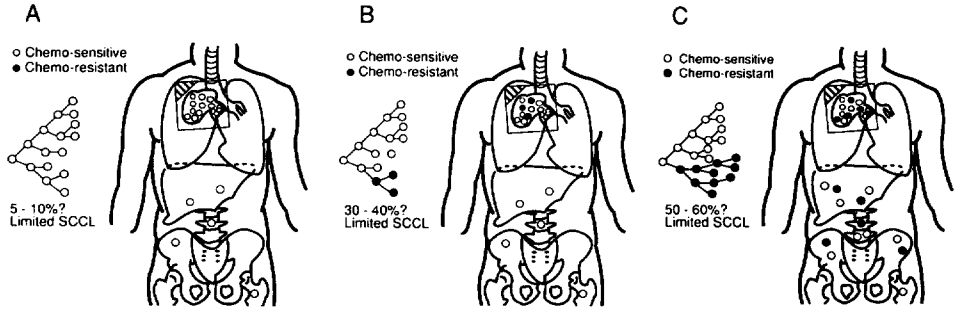

Fig 5. Conceptual model of limited-stage SCLC shows 3 patient groups according to the presence or absence of chemoresistant tumor stem cells and their location. Disease depicted outside the chest is undetectable by staging procedures. Chemoresistant disease (A) absent; (B) localized; and (C) disseminated.

metastatic process may not be controlled even if the tumor is responding to systemic therapy. Chemoresistant clones may continue to disseminate hematogenously. Even viable chemosensitive tumor may spread during ongoing chemotherapy and prosper in the pharmacologic sanctuary beyond the blood-brain barrier. Prophylactic cranial irradiation at the dose of 25 Gy in 10 fractions over 2 weeks does not reliably control this disease. Although changes in the timing and dose of prophylactic cranial irradiation may improve results, the importance of early TI for control of brain metastases is an important and previously unreported phenomenon. The different incidence of brain disease did not account for the survival differences between the two arms, as even if all patients with first recurrence in brain only are removed from the analysis, the early TI arm still has a superior survival to the late TI arm (P = .012).

Local recurrence was a problem of equal frequency in both arms of this study and occurred as first evidence of treatment failure in approximately 30% of all patients or approximately 40% of relapses. The cumulative risk of local recurrence exceeded 50% beyond 3 years. This trial used a parallel-pair technique and a thoracic radiotherapy dose of 40 Gy in 15 fractions over 3 weeks, with shielding of spinal cord after 35 Gy. More sophisticated oblique-field radiotherapy techniques avoid reduction of tumor dose associated with posterior spinal cord shielding. However, these methods would expose more pulmonary tissue to irradiation, and anthracycline-containing chemotherapy administered immediately after TI may cause a higher risk of pneumonitis. More intense up-front thoracic radiotherapy can be safely given with EP.[3,5] Randomized trials are currently in progress to determine whether intensive early TI can change the survival of limited-stage SCLC patients.

A meta-analysis of randomized comparisons of chemotherapy alone versus combined modality therapy for limited SCLC[19] did not identify an optimal time for TI. In general, the trials that showed no benefit administered TI after a sequence of chemotherapy treatments, and trials that showed an advantage for combined modality therapy administered TI relatively early in protocols designed to maintain chemotherapy intensity (Table 6). However, the positive studies had a greater capacity to detect differences because they included more patients.The trial by Perry et al[17] from Cancer and Leukemia Group B deserves special comment, because it also examined the issue of TI timing. In this study, patients were randomized to receive either chemotherapy alone (cyclophosphamide, etoposide, and vincristine), TI concurrently with the first cycle of chemotherapy, or radiotherapy concurrently with the fourth cycle of chemotherapy (week 9). Both arms that included TI had significantly superior response rates, time to progression, and overall survival rates compared with chemotherapy alone. However, no significant differences were found between the initial and delayed TI arms. This result may be explained by increased toxicity of combined modality therapy (chiefly neutropenia) resulting in marked chemotherapy dose reductions in the initial TI arm. Although randomized trials have not shown an advantage for intensive versus standard chemotherapy dosing for SCLC,[29-31] it is not difficult to demonstrate a detrimental

Table 6. Randomized Trials of Chemotherapy Alone Versus Combined Modality Therapy in Limited-Stage SCLC Showing Relationship Between Starting Time of TI and Survival Advantage

		TI			Survival				
					Median (months)		2-Year (%)		
Reference	Drugs	Start Time	Dose	No. of Patients	CTX	CMT	CTX	CMT	P
Negative studies									
Fox et al, 1985[7]	CAV	Week 10	40 Gy/20 F	73 (CR + PR)	15	16.5	10	22	NS
Souhami et al, 1984[8]	AV/CM	Week 13	40 Gy/20 F	130 (CR + PR + SD)	12	13	12	14	NS
Osterlind et al, 1986[9]	CMVL	Week 6, 10	40 Gy/20 F	145 (All)	11.5	10.5	12	5	NS
Kies et al, 1987[10]	VMEAC	Week 12, 17	48 Gy/22 F	93 (CR)	16.0	16.0	25	35	NS
Nou et al, 1988[11]	CAVML	Week 12	40 Gy/20 F	56 (All)	14.8	15.4	17	24	NS
Carlson et al, 1991[12]	POCC/VAM	Week 25 or 40	55 Gy/30 F	48 (CR + PR + SD)	20.3	18.9	40	40	NS
Positive studies									
Perez et al, 1984[13]	CAV	Week 5, 8, 11	40 Gy/14 F	291 (All)	10.5	12.5	16	24	.04
Greco et al, 1986[2,14]	CAV ± PtE	Week 1, 2, 6	45 Gy/15 F	369 (All)	10.5	12.0	21	29	< .05
Bunn et al, 1987[15]	CML/VAP	Week 1	40 Gy/15 F	96 (All)	11.6	15.0	12	28	.035
Creech et al, 1988[16]	CML	Week 8	50 Gy/25 F	310 (CR, PR)	14.0	17.0	13	19	.003
Perry et al, 1987[17]	CAEV	I: Week 1	50 Gy/25 F	399 (All)	13.6	13.1	8	15	.009
		II: Week 9	50 Gy/25 F			14.6		25	

Abbreviations: C, cyclophosphamide; M, methotrexate; L, lomustine; V, vincristine; A, doxorubicin; P, procarbazine; Pt, cisplatin; E, etoposide; F, fractions; CTX, chemotherapy alone; CMT, combined modality therapy; SD, stable disease; NS, not significant.

effect by decreasing chemotherapy intensity below standard levels.[32] The benefits of early TI in other trials in Table 6 probably were decreased by chemotherapy delays and dose reductions from actual or anticipated toxicity caused by the interaction of radiotherapy with anthracyclines, nitrosoureas, or cyclophosphamide. Chemotherapy given after TI in the early arm of our trial resulted in an increase in esophagitis, dermatitis, and anemia, but overall toxicity of concurrent EP and radiotherapy was manageable and did not compromise subsequent systemic treatment. In addition to avoiding chemotherapy interruptions, there may be other therapeutic effects associated with concurrent chemotherapy and irradiation[33] as compared with sequential therapy, but since both arms in our study received concurrent therapy, the difference in outcome is clearly due to the timing factor.

Although the majority of patients with limited-stage SCLC continue to die, the advantages of early TI are clinically important, as the chance for cure is increased. The paradigm of a medical oncologist administering a course of chemotherapy to a limited-stage SCLC patient and subsequently referring the patient to a radiation oncologist for consolidative radiotherapy no longer offers the best standard of care. These patients require consultation from both medical and radiation oncology disciplines as soon as possible after the diagnosis is made. This should facilitate the conduct of clinical trials.

Moreover, this trial may demonstrate a general oncologic principle that can be applied to the combined modality therapy of other cancers: when a tumor with a high probability of drug resistance is treated with potentially curative systemic and local modalities, early use of local therapy that does not compromise systemic treatment should decrease the chance of tumor dissemination and increase the proportion of cures.

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APPENDIX

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