

# Long-Term Survival in Limited-Stage Small Cell Lung Carcinoma

*Experience in Rochester, New York From 1975 to 1981*

T. K. GEORGE, MD,\* DENIS FITZGERALD, MD,\* BRUCE S. BROWN, MD,† CHRISTY CHUANG, PhD,‡  
ROBERT F. ASBURY, MD,\* AND LASZLO BOROS, MD\*

All patients with limited-stage small cell lung carcinoma (SCLC) diagnosed between January 1975 and 1981 in Rochester, New York, were collected. One hundred one patients were evaluable. By reviewing an entire community's experience with long follow-up, we were able to describe the response rates and survival in a large unselected population and compare them to results from concurrent cooperative group studies. Median survival for the entire group was 51 weeks, with only 18% alive at 130 weeks. There was no evidence for improvement in response or survival during the 6 years of study. Treatment results in the community as a whole were no different from that seen with cooperative group studies. A group who had initial surgery followed by adjuvant therapy had a significantly better survival and more long-term survivors than those not receiving surgery, but rare long-term survivors were seen with all treatment categories. Except for this small surgical subgroup, no other characteristics could be identified which were predictably associated with long-term disease-free survival. The overall poor survival of patient with localized SCLC suggests a need for the development of novel initial approaches to therapy.

*Cancer* 58:1193-1198, 1986.

SINCE RESULTS of the British Medical Research Council Study were published in 1973,<sup>1</sup> chemotherapy alone or in combination with radiation therapy has become the standard therapy for small cell lung carcinoma (SCLC). Complete response rates for limited stage disease have ranged from 40% to 100% with regimens employing chemotherapy with or without radiation therapy. Despite these impressive results, the proportion of long-term survivors is only 10% to 13% for limited disease, and 2% to 3% for extensive disease.<sup>2-6</sup> Because of these results, treatment of SCLC has been an active area of research in the Eastern Cooperative Oncology Group (ECOG) and other large cooperative oncology groups.

The vast majority of patients with SCLC are managed by community- and hospital-based oncologists who employ treatment programs based on the results of large cooperative group trials. There is little data available to suggest that the results obtained by large cooperative oncology groups can be duplicated in an unselected community-based population that may be older, more infirm, or have more co-existing illnesses. Rochester, New York offers an excellent model to study this issue, since all of its hospitals actively participate in ECOG studies. In addition, there is a large cohort of similar patients treated by the same hospital-based oncologists who did not participate in an ongoing ECOG study. A recent analysis has found that patients with acute leukemia who were treated on ECOG studies had a significantly better survival than similar patients who were not in the study; however, study patients had better prognostic features than those not on study.<sup>7</sup> In order to see if similar results would occur in a more common neoplasm, SCLC, we studied an entire community's experience with limited-stage SCLC over a 6-year period. The goals of the study were to determine response rates, and to identify those factors which were associated with long-term survival. The results obtained from the community study were then compared to the

From the \*Department of Medicine, The Genesee Hospital and The University of Rochester Cancer Center; †The Division of Biostatistics, University of Rochester Cancer Center, and the ‡Department of Pathology, The Genesee Hospital, Rochester, New York.

Supported in part by US Public Health Service Research Grants CA 11198 and CA 11083; American Cancer Society Grant #05435 and generous donations from our patients.

Address for reprints: Laszlo Boros, MD, The Genesee Hospital, 224 Alexander Street, Rochester, NY 14607.

The authors thank Mrs. Sheila Hutchings for her expert help in preparing this manuscript.

Accepted for publication January 8, 1986.



TABLE 1. Patient Characteristics and Follow-Up\* (101 Cases)

Characteristics	n
Sex	
Male	66
Female	35
Age (yr)	
31-40	2
41-50	12
51-60	29
61-70	39
71-80	14
>80	5
On ECOG protocol	22

\* Mean follow-up: 194.5 weeks.

published results of concurrent ECOG studies<sup>8-10</sup> that used similar treatment programs.

### Materials and Methods

Through listings available in the Rochester Regional Tumor Registry (RRTR) and the individual hospitals in Rochester, New York, we were able to review treatment and survival of virtually all patients in this community with limited-stage SCLC. The names of all patients seen at the five hospitals in Rochester between January 1975 and January 1981 with SCLC were obtained. Limited disease was defined as disease confined to one hemithorax with or without ipsilateral hilar, supraclavicular, or mediastinal lymph node involvement and without pleural effusions. Patients were required to have had a history, physical examination, serum chemistries, bone scan, and histologic or cytologic studies for review. In addition, 58% had a bone marrow examination, 75% had a CT scan, ultrasound, or nuclear scan of the liver, and 77% had a CT or nuclear scan of the brain. All of the cases were reviewed for accuracy by one of the authors (B.B.), who confirmed the original diagnosis in 94%. Limited disease was more strictly defined for ECOG protocols. Those patients could not have positive supraclavicular lymph nodes and must have had negative liver scan, brain scan, and bone marrow biopsy findings in addition to the other tests.

Five hundred sixteen cases were entered into the registry and 484 charts were available for review. Forty-six patients were excluded because of inadequate staging or evaluation. Two hundred eighty-seven patients were excluded because of extensive disease and were not further analyzed. One hundred one patients met all criteria and were considered evaluable. The remaining patients were excluded because of improper entry into the registry (17), second malignancy (3), death within 1 week of diagnosis (13), refusal of therapy (1), no pathology available for review (12), mixed small cell and non-small cell carcinoma (4), and non-small cell lung cancer (2).

Treatment was divided into courses. Course 1 consisted of the entire treatment used in the initial attempt to achieve response prior to relapse or progression. Subsequent courses consisted of treatments attempting to attain a response after failure in Course 1. Four treatment types were defined: surgery (SURG), chemotherapy (CT), radiation therapy (RT), and combined therapy (CT/RT). If surgical resection was performed, these patients were recorded as SURG regardless of whether they received adjuvant therapy. Any combination of chemotherapy and radiation therapy without surgery was coded as CT/RT. The CT and RT groups included those patients treated only with that modality.

Response was recorded as complete (CR), partial (PR), stable or no response (NR), or progression (PROG) based on standard ECOG criteria as determined by the treating physician at the time. Those patients who underwent surgical resection as part of Course 1 with all known tumor removal were automatically recorded as CR.

Survival was defined as date of diagnosis to date of death, or, if alive, to last date of follow-up. Long-term survivors were those patients alive longer than 2.5 years (130 weeks).

Chi-square test<sup>11</sup> was used to compare the response rates and the distributions of patient characteristics in the various strata defined by the studied factors. Fisher's exact test<sup>11</sup> was used when the cell frequencies were small. The *P* values reported for these tests were for two-sided tests. Survival curves were estimated by Kaplan-Meier's product-limit method,<sup>12</sup> and compared using Mantel-Cox<sup>13</sup> (generalized Savage) test. To adjust for the effects of covariates in comparing survival, Cox's regression model<sup>14</sup> was employed. Likelihood ratio tests were used on the results from fitting Cox's models. In this study, significance was set at the 0.05 level for all comparisons.

### Results

Age, sex, entry on ECOG protocol, and follow-up are included in Table 1. Sixty-eight percent were between 50 and 70 years of age, and 22% participated in ECOG studies. Mean follow-up for the patients remaining alive was 194.5 weeks. Only one patient had follow-up less than 143 weeks.

Thirteen patients were treated in the SURG group, 43 in the CT group, 20 in the RT group, and 25 in the combined modality group. Of the 13 patients in the SURG group, 10 received adjuvant chemotherapy and 2 received only adjuvant radiation therapy. Only one SURG patient received no additional treatment.

Similar chemotherapy regimens were used in the CT and CT/RT group. Of the 63 patients who received chemotherapy, the most common regimens were cyclophosphamide, CCNU, and methotrexate (21); cyclophosphamide,



TABLE 2. Treatment Type and Response

Treatment	n	Response			
		CR (%)*	PR	NR	PROG†
Course 1					
SURG‡	13	12 (92)	0	0	1
CT	43	5 (12)	11	7	20
RT	20	11 (55)	2	3	4
CT/RT	25	12 (48)	10	1	2
Total	101	40 (40)	23	11	27
Course 2					
CT	23	0	1	8	20
RT	18	3 (17)	5	8	3
Total	41	3 (7)	6	16	23
Course 3					
CT	19	0	1	4	11
RT	6	1 (17)	3	0	1
Total	25	1 (4)	4	4	11

\* CR among CT, RT and CT/RT in course 1 was significantly different at  $P < 0.001$ .

† Patients who were not evaluable due to intercurrent death, no repeat x-ray or physical examination, or those lost to follow-up were coded as progression.

‡ One patient in SURG had incomplete follow-up and was therefore coded as PROG.

CR: complete response; PR: partial response; NR: no response; PROG: progression; SURG: surgery; CT: chemotherapy; RT: radiation therapy; CT/RT: combination therapy.

mide, methotrexate, vincristine, and procarbazine (12); cyclophosphamide and CCNU (8); and cyclophosphamide, doxorubicin, and vincristine (5). Response rate and survival did not correlate with any drug or drug combination.

Table 2 lists the number of patients treated and the response for each treatment group in the first three courses as defined under methods. The overall CR rate for Course 1 was 40%. The CR rate excluding the SURG group was 32%. One death occurred as a result of gastrointestinal (GI) bleeding, and 5 other life-threatening toxicities (thrombocytopenia [2], leukopenia, diarrhea, and infection) occurred during treatment. Toxicity appeared to be no greater for the CT/RT group, although the one death that did occur was in a patient receiving concurrent radiation and chemotherapy.

Response to treatment after progression in Course 1 was poor. (Table 2) Only four CR and ten PR were seen in Courses 2 and 3. All CR and eight PR were the result of local chest radiation. Only 5% of chemotherapy-treated patients responded in each course to second- and third-line regimens.

Figure 1 shows overall survival. Median survival for the entire group was 51 weeks. Eighteen percent were alive at 130 weeks (2.5 years), with the longest survivor alive at 275 weeks. Survival was separately analyzed by age, sex, hospital, year of treatment, treatment on or off ECOG

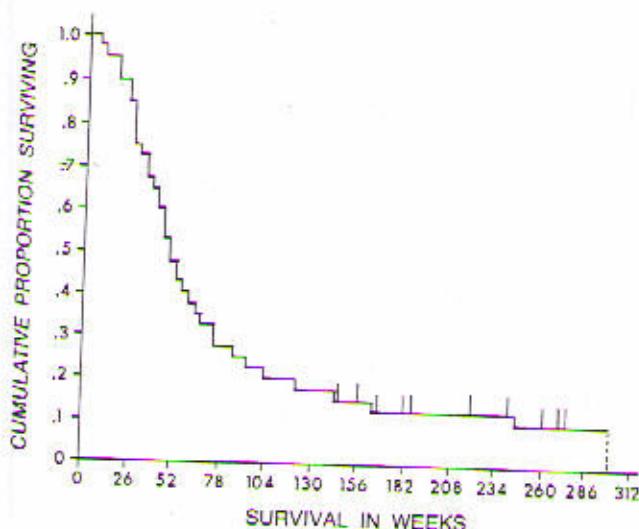


FIG. 1. Cumulative proportion surviving versus time (101 patients). Vertical marks indicate patients remaining alive.

protocol, and whether patients received prophylactic brain irradiation. None of these factors significantly influenced survival. There was no trend suggesting patients treated in later years had better survival than those treated in earlier years.

Figure 2 shows survival according to response. As expected, those attaining a CR had a significantly better survival compared to other groups ( $P < 0.0001$ ). Median survival for the CR group was 84.7 weeks versus 46.3 weeks for the PR group, 44.7 weeks for the NR group, and 34 weeks for the PROG group. Survival for the PR group did not differ from the NR or PROG groups.

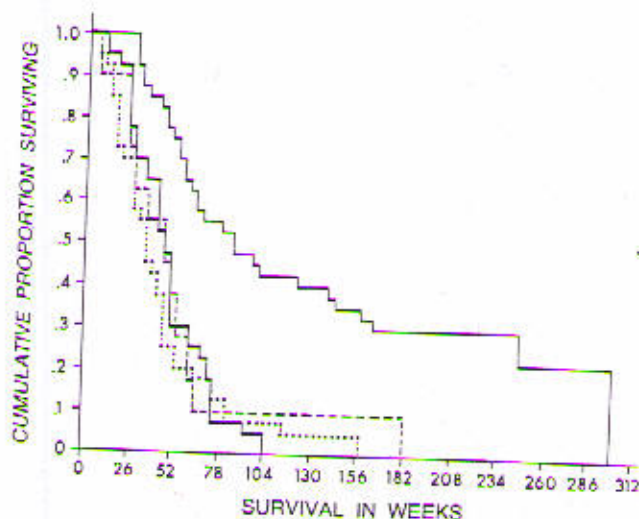


FIG. 2. Cumulative proportion surviving versus time. CR (light solid line), PR (heavy solid line), NR (broken line) and PROG (dotted line). The difference between CR vs PR, NR and PROG is significant ( $P < 0.0001$ ).



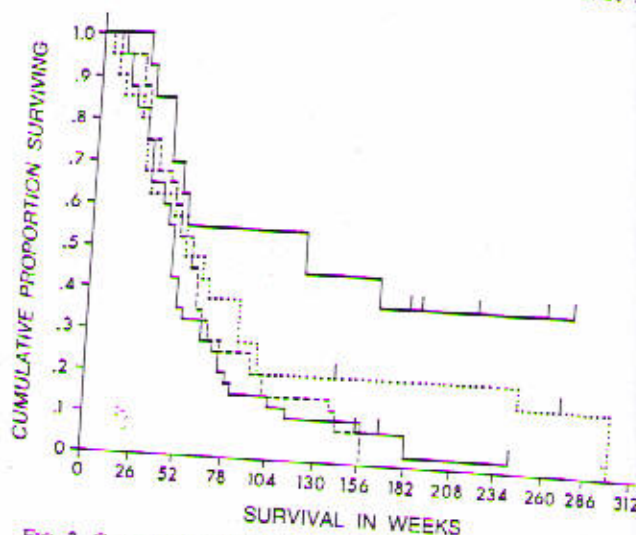


FIG. 3. Cumulative proportion surviving versus time. SURG (heavy solid line), CT (light solid line), RT (dotted line), and CT/RT (broken line). The survival advantage of the SURG group is significant ( $P = 0.028$ ). Vertical marks indicate patients remaining alive.

Survival with the various treatment types is shown in Figure 3. There was a significant survival advantage in favor of the SURG group ( $P = 0.028$ ). Median survival for the SURG group was 123.1 weeks versus 47.6 weeks for the CT group, 53.7 weeks for the RT group, and 56.4 weeks for the CT/RT group. When comparing the entire survival curve (Mantel-Cox analysis) rather than median survival, SURG was not significantly better than RT, while there was a significant difference in the survival time

TABLE 3. Long-Term Survivors\*

Characteristics	n
Sex	
Male	11
Female	7
Age	
31-40	0
41-50	4
51-60	4
61-70	6
>70	4
Treatment type	
SURG	6
CT	4
RT	4
CT/RT	4
Clinical stage	
I†	10
II	0
III	8
Total	18

\* Alive > 2.5 years.

† 6/10 were from SURG group.

comparing SURG and CT ( $P = 0.007$ ) and SURG and CT/RT ( $P = 0.017$ ). These differences in survival remained when we compared survival using sex, PS as covariates in Cox's regression models. When we compared survival of the SURG group to all other patients not having had surgery (NO SURG), the SURG group had a significantly longer survival ( $P = 0.009$ ). The median survival for the SURG group was 123.1 weeks versus 47.6 weeks for the NO SURG group.

Characteristics of the 18 patients alive longer than 2.5 years are shown in Table 3. The patient characteristics were reflective of the group as a whole. There were patients in each age grouping, including four patients older than 70 years. Six (33%) patients had surgery as part of their initial treatment course. All of the long-term survivors in the SURG group had only a peripheral nodule on their chest radiograph at presentation. Two were found to have a second nodule at surgery. None of the six had metastases to local or regional lymph nodes. Among the other long-term survivors, 4 had larger central masses (>2 cm in diameter) without apparent hilar node metastases. In the remaining eight patients had hilar masses, and in the absence of surgical staging, it was not possible to determine if they had regional node involvement. Four long-term survivors were found in each of the three NO SURG groups. Of the four who had CT alone, two received cyclophosphamide and CCNU (one for 12 weeks and the other for an uncertain period of time), a third received cyclophosphamide, CCNU, and methotrexate (36 weeks), and the fourth received procarbazine, cyclophosphamide, vincristine, methotrexate (60 weeks) and doxorubicin (27 weeks). Of the four who had CT/RT, three were given concurrent treatment. One received cyclophosphamide (single dose), another received cyclophosphamide and CCNU (60 weeks), and the third received cyclophosphamide, vincristine (48 weeks) and doxorubicin (27 weeks). Only two long-term survivors received prophylactic whole brain irradiation (one SURG and one CT/RT).

### Discussion

We undertook this study to see whether results reported for treatment of limited-stage SCLC according to strictly controlled protocols was different from that seen in the community as a whole. During the 6-year period of our analysis, the five hospitals in Rochester, New York, treated patients both on and off ECOG studies. The chemotherapy programs used for non-study patients were similar to those employed in the ongoing ECOG study. The interesting outcome of our analysis was the lack of difference between the two groups with regard to response and survival. The 12% CR rate and 26% PR rate seen in the chemotherapy-treated patients compare well with the 9% CR rate and 38% PR rate of the limited-stage patients in



the concurrent ECOG studies of SCLC.<sup>9</sup> Furthermore, the median survival of 47.6 weeks for the CT group was slightly better than the median survival of 35 weeks reported for the same two ECOG studies<sup>9,10</sup> that were in progress during the 6-year study period. The 22 patients who participated in ECOG studies had an overall survival that was not different from the nonparticipants, although none of the long-term survivors happened to be on an ECOG study.

The CR rate in our study of 40% and the overall response rate of 63% is in keeping with published data for the treatment of limited-stage disease.<sup>4</sup> Our inability to demonstrate a significant survival advantage for patients attaining a PR versus NR or PROG may be due to the difficulty in defining PR, especially in a retrospective study. This lack of advantage has been noted by others.<sup>1</sup>

Particularly discouraging was the lack of response with second-line chemotherapy. (Table 2) Of patients treated with chemotherapy who had failed prior therapy, no CR and only two PRs were seen. As reviewed by Morstyn *et al.*,<sup>4</sup> many studies have failed to show any significant response when Phase II agents were used for previously treated patients. Our data suggest that for those patients with locally recurrent disease, radiation therapy may be the treatment of choice. Although a recent report suggests that combinations of cisplatin and etoposide offer some palliation in patients refractory to initial therapy,<sup>15</sup> the routine use of other drug combinations may not be warranted.

Our long-term survival was 18%. When we excluded the group that had surgery as part of their initial treatment, long-term survival dropped to 12%. These figures are in keeping with published data.<sup>4,16</sup> Interestingly, four long-term survivors were older than 70 years of age. Although Davis and colleagues<sup>6</sup> have noted an adverse impact on age, our results support other reports<sup>4</sup> that age by itself should not be used to exclude patients from treatment with curative intent.

The significant survival advantage for the SURG group was not surprising, since these patients all had a minimal tumor burden. Harper *et al.*<sup>17</sup> have shown that patients with small intrathoracic tumors (<30 cm<sup>2</sup> in total area) survive longer than those with larger tumors and that the likelihood of distant metastasis is smaller. Shepherd *et al.*<sup>18</sup> were able to show a survival advantage for a group of patients with "very limited" SCLC. Since all but one of our SURG patients also received adjuvant chemotherapy or radiation therapy, we cannot comment on the need for such adjuvant treatment. Nevertheless, it is intriguing to postulate that surgery alone may have cured some of our patients. There is evidence in the earlier British Medical Research Council Study,<sup>1</sup> where a small percentage of patients were cured by resection alone, and more re-

cently in the study reported by David *et al.*<sup>6</sup> that survival without adjuvant treatment is possible for a highly selected subset of operable patients with SCLC. Unfortunately, it is presently impossible to choose which patients would be candidates for minimal treatment, and the small number of such patients discourages any prospective study of adjuvant treatment.

There is no doubt that some patients with SCLC are cured with nonsurgical treatment. Twelve of our long-term survivors received chemotherapy, radiation therapy, or both. The appropriate duration and intensity of nonsurgical treatment remains to be defined; however, the ability to achieve long-term survival in 12% of these patients is certainly a modest achievement. Eight patients in the CT/RT group were treated with concurrent CT and RT, and these were long-term survivors. Cooperative group trials continue to look at combined CT and RT, including concurrent CT and RT. Although CR rates appear to be higher, it is at the expense of increased toxicity. The one death in our study occurred in the subset of the CT/RT group that received concurrent CT and RT. Emphasis is currently being placed on minimizing these toxicities while maintaining the higher response rates.

We conclude that the results reported by large cooperative oncology groups in the treatment of SCLC can be duplicated by community oncologists using similar therapeutic programs. We identified a subset of patients who, when treated surgically with adjuvant therapy, have a higher likelihood of long-term survival, but the need for adjuvant therapy in that setting is yet to be confirmed. There was no evidence for significantly improved survival during the 6-year period of our study in Rochester.

With only modest CR rates, ineffective long-term palliation, and few disease-free survivors beyond 2 to 3 years, no treatment can be considered as standard for patients with limited stage small cell lung cancer. Many fruitful areas of research remain. In view of the poor response seen after failure of the initial treatment approach, more investigational studies should be conducted in untreated patients. We agree that more effort should be directed toward accelerating the inclusion of new agents in primary chemotherapy combinations. Some patients should be treated with investigational agents first, reserving the "standard" treatment for those who do not respond. Some investigators using this approach have identified new drugs, such as carboplatin, which have significant antitumor activity in untreated patients.<sup>19</sup> If new agents are given only to relapsed patients, drugs such as etoposide, which have significant activity when used initially, might be abandoned based on lack of response in Phase II studies of previously treated patients.<sup>20</sup> It is only through the use of such innovative approaches that further progress in the treatment of SCLC will occur.



## REFERENCES

1. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus: Ten year follow-up. *Lancet* 1973; 2:63-65.
2. Hansen M, Hansen HH, Dombernowsky P. Long-term survival in small cell carcinoma of the lung. *JAMA* 1980; 244:247-250.
3. Ginsberg SJ, Comis RL, Gottlieb AJ *et al*. Long-term survivorship in small cell anaplastic lung carcinoma. *Cancer Treat Rep* 1979; 63: 1347-1349.
4. Morstyn G, Ihde DC, Lichter AS *et al*. Small cell lung cancer 1973-1983: Early progress and recent obstacles. *Int J Radiat Oncol Biol Phys* 1984; 10:515-539.
5. Livingston RB, Stephens RL, Bonnet JD, Grozea PN, LeLane DE. Long term survival and toxicity in small cell lung cancer. *Am J Med* 1984; 77:415-417.
6. Davis S, Wright PW, Schulman SF, Scholes D, Thorning D, Hammar S. Long-term survival in small cell carcinoma of the lung: A population experience. *J Clin Oncol* 1985; 3:80-91.
7. Boros L, Chuang C, Butler FO, Bennett JM. Leukemia in Rochester (NY): A 17-year experience with an analysis of the role of Cooperative Group (ECOG) Participation. *Cancer* 1985; 56:2161-2169.
8. Edmonson JH, Lagakos SW, Selawry OS *et al*. Cyclophosphamide and CCNU in the treatment of inoperable small cell carcinoma and adenocarcinoma of the lung. *Cancer Treat Rep* 1976; 60:925-932.
9. Ettinger DS, Lagakos S. Phase III Study of CCNU, cyclophosphamide, Adriamycin, vincristine and VP16 in small cell carcinoma of the lung. *Cancer* 1982; 49:1544-1554.
10. Vogl SE, Mehta C. Standard vs. intensive induction chemotherapy of the small cell bronchogenic carcinoma with cyclophosphamide, CCNU and methotrexate, followed by continuous CCNU or cyclic maintenance therapy (Abstr). *Proc Am Assoc Cancer Res* 1981; 22:199.
11. Snedecor GW, Cochran WG. Statistical Methods. ed. 7. Ames, Iowa: Iowa State University Press, 1980.
12. Kaplan EL, Meier P. Nonparametric Estimation From Incomplete Observations. *J Am Stat Assoc* 1958; 53:457-481.
13. Dixon WJ, Brown MB, Engelman L *et al*. BMDP Statistical Software. Los Angeles, California: University of California. Press, 1981.
14. Cox DR. Regression Models and Life Tables. *J R Stat Soc [Ser. B]* 1972; 34:187-220.
15. Evans WK, Osoba D, Feld R, Shepherd FA, Bagois MJ, DeBoer G. Etoposide (VP-16) and cisplatin: An effective treatment for relapse in small cell lung cancer. *J Clin Oncol* 1985; 3:65-71.
16. Comis RL. Small cell carcinoma of the lung. *Cancer Treat Rev* 1982; 9:237-258.
17. Harper PG, Souhami RL, Spiro SG *et al*. Tumor size, response rate, and prognosis in small cell carcinoma of the bronchus treated by combination chemotherapy. *Cancer Treat Rep* 1982; 66:463-470.
18. Shepherd FA, Ginsberg R, Evans WK, Haddad R, Feld R, DeBoer G. 'Very limited' small cell lung cancer (SCLC): Results of nonsurgical treatment (Abstr). *Proc Am Soc Clin Oncol* 1984; 3:223.
19. Smith IE, Harland SJ, Robinson BA *et al*. Carboplatin: A very active new cisplatin analog in the treatment of small cell lung cancer. *Cancer Treat Rep* 1985; 69:43-46.
20. Asbury RF, Rubins J, Bennett J. Etoposide in small cell lung cancer resistant to prior chemotherapy. *Cancer Treat Rep* 1983; 10:951-952.

## Chemotherapy Foundation Symposium VII

Chemotherapy Foundation Symposium VII "Innovative Cancer Chemotherapy for Tomorrow" at the Sheraton Centre Hotel in New York, November 12-14, 1986 is presented by the Division of Medical Oncology, the Department of Neoplastic Diseases and the Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY). Registration fees are \$300 for physicians and \$75 for House Staff, Fellows, and other health care professionals. Registrants are eligible for 20 hours in Category 1 of the Physician's Recognition Award of the AMA and 20 cognates, Formal Learning by ACOG. Dr. Ezra M. Greenspan is chairman of the meeting.

Direct inquiries to: Director, Page and William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737 or 650-6772 for further information.