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Small-cell Lung Cancer

A Curable Disease

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Many studies have been initiated over the past 5 years to determine whether or not small-cell lung cancer can be cured. The purpose of this review is to update and examine the data indicating that small-cell lung cancers can be cured by aggressive therapy. We will examine the results from other series dealing with small-cell lung cancer and present a follow-up report on our own patients.

It is now clearly evident that small-cell lung cancer is a disseminated neoplasm that has its genesis in the bronchial epithelium and submucosa of middle-aged smokers. These cancers generally arise in the perihilar region, grow rapidly, and produce symptoms by way of local invasion or by distant metastasis. Small-cell cancers have a higher growth fraction and a more rapid replication rate than the other types of lung cancer and as a consequence are more sensitive to both chemotherapy and radiotherapy. The clinical behavior of this cancer is sufficiently different from other types of lung cancer to make it a distinct entity.

The behavior of small-cell lung cancer as a distinct clinicopathologic entity was first appreciated when the surgical results for this tumor were examined. Although the tumor could be extirpated in approximately one-fourth of the patients presenting with what appeared to be limited disease, none of the patients survived 5 years after surgery [21]. A similar result was obtained when the local tumor mass was treated with radiotherapy alone [1, 7, 17, 18, 20]. As many as one-third of the local tumors in the chest were eradicated by aggressive radiation therapy, but the patients generally died of distant metastasis after completion of the regional radiotherapy. These results and clinical and pathological findings indicated that small-cell lung cancer was a disseminated disease at the time of diagnosis in the vast majority of patients and that local-regional therapy (surgery and/or radiotherapy) was not much better than no treatment with respect to survival at 2 years [22] (Table 1).

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These early studies were also useful in determining a rudimentary staging system for small-cell lung cancer. This staging system is relatively simple with patients designated as having *limited-stage* disease, in which the tumor is limited to one hemithorax and encompassable in a single radiotherapy field. Those individuals with detectable disease elsewhere are designated as having *extensive-stage* disease. For the purpose of this review, we will examine only the results in the treatment of limited-stage small-cell lung cancer. Current results in extensive-stage disease indicate that less than 5% of these patients survive longer than 2 years and many survivors still have residual cancer [11]. Therefore, extensive-stage small-cell lung cancer has a very low 'cure rate' with existing modalities, and new approaches are being tried. The rest of this review will concentrate on the treatment of limited-stage small-cell lung cancer.

Small-cell lung cancer is generally staged by the tests listed in Table 2. About one-third of the patients presenting with small-cell lung cancer will have limited-stage disease. Since this cancer accounts for approximately 20% of all cases of lung cancer at least 7,000 new patients with limited-stage small-cell lung cancer are diagnosed yearly in the United States.

In treating patients with limited-stage small-cell lung cancer it became apparent in the very early studies that although the cancer appeared to be 'limited' by clinical examination neither surgery nor local radiotherapy could cure the disease. As the results in Table 1 indicate, local modalities of treatment did not yield significant numbers of survivors 2 years after the initiation of therapy. Therefore, first single drugs and later multiple combinations of antineoplastic agents were used in conjunction with local radiotherapy in an attempt to improve the complete response rate and thus the survival of patients with this disease. Radiotherapy has been retained by most investigators because of its known efficacy as a single modality in eradicating the local-regional disease in about a third of the patients. Chemotherapy was added in an attempt to

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Table 1. Results in the treatment of limited-stage small-cell lung cancer[a]

Investigator[a]	Therapy	No. of patients	CR (%)	Median surv.[c] (weeks)	One-year surv. (%)	Relapse-free surv. 2 years (%)
Wolf [22]	None	31	–	14	7	0
Mountain, MD Anderson [21]	Surgery[b]	187	25	20	20	0
Various RT series [7, 17, 18, 20, 21]	Local RT	235	40–65	25	20	< 5
Bergsagel [1]	RT, CTX	27	–	31	38	–
Holoye, MD Anderson [15]	RT, CTX, VCR	16	50	50	50	19
Livingston, SWOG [19]	RT, CTX, ADR, VCR	108	41	52	50	15
Einhorn, Indiana [6]	RT, CTX, ADR, VCR, CCNU, MTX, BCG	19	89	78	80	26
Israel, Paris [16]	CTX, ADR, CCNU, MTX, VCR Bleo, Emetine, *C. parvum*	20	70	–	–	25
Jackson, Bowman Gray (personal communication)	RT, CTX, ADR, VCR, CCNU, MTX	12	–	–	–	17
Hansen, Copenhagen [14]	RT, CTX, CCNU, MTX, VCR	110	–	–	–	11
Brereton, NCI [3]	RT, CTX, ADR, VCR	10	100	84	–	40
Eagan, Mayo Clinic [5]	RT, CTX, VP-16	12	40	13	–	25
	RT, ADR, VP-16	9	33	12	–	11
Cohen, NCI–VA [4]	CTX, MTX, CCNU, ADR, VCR, Procarb	19	74	65+	–	16
Bitran, Univ. Chicago [2]	RT, CTX, ADR, VCR, MTX	12	100	–	–	17
Ginsberg, Syracuse [8]	RT, CTX, VCR, CCNU, ADR, HEXA	36	64	–	–	22
Greco, Vanderbilt [11–13]	RT, CTX, ADR, VCR, HEXA, VP-16, MTX ± *C. parvum*	32	94	68	72	25

[a] Some of these end results were updated by personal communication with the investigator [10]
[b] CR in surgery refers to complete resection of all apparent disease – median survival was the same for resectable and unresectable patients in this series
[c] Survival

improve local control and also to improve the control of distant micrometastasis. To date, however, there is no proof that local radiotherapy is additive to chemotherapy with respect to survival at two years.

The sequence of success for the use of chemotherapy in a disseminated neoplasm is illustrated in Table 3. It is important to recognize that the treatment of certain cancers can go through this sequence, resulting in some long-term survivors with little change in the *median* survival. The former is a result of effective therapy for a subgroup of the patients and the latter more a measure of progress in the whole group of patients. It is important to view most studies in the context of both measures. The early results with small-cell lung cancer indicated that those patients who achieved a partial response did not survive much longer than those who did not respond. As Table 1 demonstrates, higher doses of more drugs used in conjunction with local radiotherapy increased the complete response rate and improved survival. Table 1 is a compilation of results from different investigators in different institutions utilizing combination chemotherapy, generally with regional radiotherapy and sometimes with immunotherapy

Table 2. Pretreatment staging evaluation

1. Physical examination
2. Chest roentgenograms
3. Fiberoptic bronchoscopy with biopsies
4. CT scan of brain
5. Radionuclide liver and bone scan
6. Bone marrow aspiration and biopsy

Table 3. Simplified sequence of chemotherapeutic success in a disseminated neoplasm

Unresponsive or poorly responsive neoplasm
Less than partial responses to available drugs
↓
Partial responses to newer active single drugs
↓
Increased partial responses and rare complete responses to some single drugs and combination chemotherapy
↓
Increased complete responses to more effective combination chemotherapy
↓
Increased survival in complete responders with or without continued treatment during remission
↓
A portion of long-term survivors are cured

in the treatment of limited stage small-cell lung cancer. The results in Table 1 clearly illustrate that chemotherapy has improved our ability to achieve a complete response in patients with this disease and this has resulted in an increased median survival as well as an increase in the 1-year survivorship for these patients [11]. More important is the fraction of patients surviving through 2 years without relapse. These data are summarized on the far right of Table 1 and illustrate that although initially very few patients treated with regional modalities survived past 2 years, the addition of even small amounts of relatively nonaggressive chemotherapy did result in some patients' living longer than 2 years without evident disease. Investigators have utilized a wide variety of drug combinations (in varying schedules and doses) with and without regional radiotherapy and more recently with prophylactic cranial irradiation in their treatment regimens. If one summarizes all these studies and looks at the actual (not actuarial) relapse-free percentage at 2 years, it is apparent that approximately 25% (range 11%–40%) of the patients with limited-stage small-cell lung cancer are alive and free of disease at 2 years. Since it is rare for a patient to relapse who is disease-free at 2 years, these results suggest that approximately one-fourth of patients with limited-stage small-cell lung cancer are currently being cured of their cancer.

In 1975 our own experience indicated that small-cell lung cancer was a highly responsive neoplasm. Early in 1976 we initiated a series of studies at Vanderbilt University Medical Center to attempt to improve the results in the treatment of this disease by combining multiple drug chemotherapy with regional irradiation therapy [10, 12, 13]. Patients were entered on this study between January 1976 and January 1979 if they had limited-stage, previously untreated, pathologically documented small-cell lung cancer (oat-cell or intermediate-cell subtypes). A total of 51 patients with limited-stage disease were entered on treatment over the 3-year period of the study. Treatment consisted of remission induction chemotherapy and simultaneous radiotherapy. Supervoltage radiotherapy was given to the region of the primary tumor, mediastinum, and supraclavicular node areas at a total dose of 3,000 rads in ten 300-rad daily fractions. The first 12 patients were not given prophylactic radiotherapy to the whole brain, but all the remaining patients received concomitant whole-brain irradiation according to the same dose and fractionation schedule as the chest radiotherapy. Each patient received cyclophosphamide 1,000 mg/m^2, doxorubicin 40 mg/m^2, and vincristine 1 mg/m^2 IV on the first day of radiotherapy and thereafter every 3 weeks for a total of six cycles. After induction therapy, a non-cross-resistant combination of the epipodophyllotoxin VP-16 (200 mg/m^2 IV on days 1 and 8 of each month) and hexamethylmelamine (8 mg/kg PO on days 1 through 14 of each month) was administered for three monthly cycles. Patients were then assigned at random to receive maintenance cyclic methotrexate (75 mg/m^2 IM every 3 weeks) or methotrexate plus *Corynebacterium parvum* (2.5 mg/m^2 SC every 2 weeks) for 7 months.

All patients were evaluated for response to therapy and extent of disease after two or three cycles of induction chemotherapy. A *complete response* was defined as disappearance of all clinical evidence of disease by physical examination, chest X-ray, and fiberoptic bronchoscopy (with biopsy, washings, and brushings). In addition to showing complete regression of the primary tumor mass and a normalized bronchoscopy, the patients in complete remission did not show clinical evidence of disease elsewhere.

The 51 patients on study have been analyzed for survival in three time frames as described below:

1) Original 16 Patients with Limited Disease. The original 16 patients were entered on study between January 1976 and January 1977 [12]. Minimum follow-up has been 34 months, with the longest surviving patient now 40 months from the time of starting treatment. Of these original 16 patients, three died of isolated brain metastasis and none had received prophylactic whole-brain radiotherapy. One patient died of a myocardial infarction while in complete remission at 5 months. Three patients (19%)

are alive and disease-free at 34+, 39+, and 40+ months. The first 12 patients were not treated with prophylactic whole-brain radiation, and although postmortems were not obtained there was no clinical evidence of disease outside the brain at the time of relapse in the three patients who died of isolated brain metastasis. Although seven of the original 16 patients were alive at 2 years (44%), only four were disease-free (25%). One of these four patients disease-free at 2 years subsequently relapsed and died at 36 months. Therefore, 3 of the 16 (19%) are disease-free at present, with median follow-up in excess of 3 years [12].

2) Limited-stage Patients Entered on Study Between January 1977 and January 1978. The next 16 patients with limited-stage small-cell cancer were entered on study in the second year of this program. These patients received prophylactic whole-brain radiation therapy in addition to the same treatment regimen given the original 16 patients. Five of these 16 (31%) patients have survived 2 years and *all* are clinically free of disease. The minimum follow-up is in excess of 25 months for these five patients. Three patients in this group died of causes not clearly related to their cancer, one with encephalitis and two with myocardial infarctions.

In summary, of the 32 patients entered over the initial 2 years of the study, eight (25%) are alive and free of disease, with a minimum follow-up in excess of 2 years. Four patients in complete remission died of diseases other than cancer (3 of myocardial infarctions and 1 with encephalitis). One additional patient died of sepsis in clinical remission but was found to have small-cell cancer at postmortem [13].

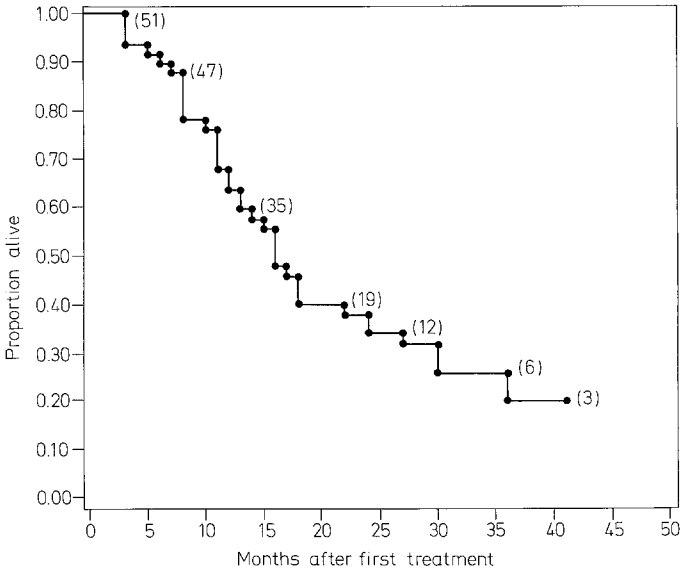

Fig. 1. Actuarial survival in limited-stage small-cell lung cancer. Figures in parentheses give number of patients surviving at each time interval

3) Additional Limited-stage Patients Entered on Study between January 1978 and January 1979. An additional 21 patients were entered in the third and final year of this study. They were treated with exactly the same therapy as described above. Since the median follow-up on this group is only 15 months it adds little to the data on 2-year disease-free survivors. However, the patients appear to have disease-free survival rates similar to the earlier groups, with five of the eight (63%) patients at risk for 14 months alive and disease-free [13].

An actuarial survival curve has been updated and includes all 51 patients on study (Fig. 1). Since this study began in January 1976 only patients from the original group of 16 have been at risk for 3 years. Five were alive at 30 months and four were disease-free (32+, 34+, 39+, and 40+ months). One died at 36 months after a late relapse at 31 months. Survival in all the patients is now in excess of 1 year, and the median follow-up is over 2 years. The *actuarial survival* curve indicates that over 30% of the patients with limited-stage small-cell lung cancer being treated will be alive 2 years after beginning therapy. Nearly all these patients are also disease-free. The actuarial curve after 30 months is only based on four disease-free patients. More follow-up time is needed to define the 3–5 year *actual* survival. It should be emphasized that the *actual disease-free* survival of patients at risk for 2 years in this series is 25% (8/32 alive and disease-free). Only those patients who achieve a complete response, as defined earlier, reach the 2-year mark disease-free. We are currently analyzing the data to see what other prognostic factors are important in predicting 2-year relapse-free survivals in patients with limited-stage small-cell lung cancer (Bihl et al. in preparation).

In summary, our results and those of the other investigators indicate that limited-stage small-cell lung cancer is indeed a curable disease for approximately 25% of the patients. Although it is currently impossible to predict which individual patient will be among the disease-free group at 2 years it appears that those with a smaller tumor burden and those who rapidly achieve a complete response (within 2–3 cycles of chemotherapy) as evaluated by re-bronchoscopy have the best chance of achieving long-term disease-free survival. Although an occasional patient will relapse after being disease-free at 2 years (1/9 at risk in our series), the vast majority of patients who are still in complete remission at 2 years have not relapsed to date and are probably cured. An occasional patient has relapsed late with lung cancer of a histological type different than their original small-cell cancer. Mixed tumors may play a role with eradication of the small-cell component and the subsequent outgrowth of the more resistant non-small-cell lung cancer at relapse. Conversely, a change in the histological cell type of the original cancer may occur. Our experience with biological markers bears on this question. Patients with ADH excess associated

with small-cell lung cancer may relapse with ADH excess (same clone) or without ADH excess (?new clone). This may indicate eradication of one clone (ADH-positive) with the outgrowth of a different clone. However, an alternate explanation in the latter group is a loss of function of the original clone.

Patients cured of small-cell lung cancer have the burden of having had the disease and of having had the treatment to carry with them for the rest of their lives. The ultimate results of treatment will only be measurable if these patients are followed for a much longer period of time [9, 20]. Because of the long history of smoking associated with the development of their small-cell lung cancer, they are at risk for a variety of other neoplasms in the tracheobronchial tree. The effect of having had a single neoplasm of this region cured by chemotherapy or chemoradiotherapy on the subsequent development of other neoplasms and on late recurrence by the original tumor is unknown.

As clinical investigators, we should not be overjoyed at the prospect of curing 25% of the patients with limited-stage small-cell lung cancer. In addition to the 75% of the limited-stage patients that ultimately die of this cancer, there are the more numerous extensive-stage patients who rarely survive 2 years disease-free. Since 75% of the limited-stage patients and 98% of the extensive stage patients (thus a total of 90% of all patients with small-cell lung cancer) ultimately die of this disease there is still a great need for further therapeutic advances in this form of lung cancer. Based on the results to date, the investigation of surgical removal of the primary tumor followed by chemotherapy, more aggressive combination chemotherapy with existing drugs and/or with new agents and the role of autologous bone marrow transplantation to achieve higher drug doses will be areas of intense and productive investigation for the 1980s.

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