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Extensive Squamous Lung Cancer
A Crack in the Door

Approximately one-half of all patients with lung cancer have extensive disease (dissemination beyond the hemithorax) at the time they are first seen by a physician. The most common histologic type continues to be squamous. Thus, the problem of the patient with extensive squamous carcinoma of the lung is a very frequently encountered one. Unfortunately, it has been a study in therapeutic frustration. Surgery obviously has no definitive role to play, and therapy with irradiation has been limited by its role as a local method to attempts at symptomatic palliation. The third major form of treating cancer, chemotherapy, has been employed with success in lung cancer only against the small-cell histologic type. This has not been for lack of effort; the Veterans Administration Lung Group has tested a variety of chemotherapeutic agents over the past 19 years in thousands of patients, as have other cooperative groups and major centers for treating cancer.

It is known that a variety of factors influence survival in such patients independent of therapy. The most powerful of these is performance status. In a control (placebo) group of 273 patients who received supportive care only as treatment for extensive squamous disease, Zelen reported a variation in median survival from 2.5 to 20 weeks; the lowest was in bedfast patients (Karnofsky performance status, 1 to 4), and the highest was in fully ambulatory individuals (Karnofsky, 8 to 10). By 36 weeks, none of the worst group and only 26 percent of the group with the best performance status were alive. If one excludes the bedfast patients, median survival with therapy with a variety of reported single agents and combinations varies from 9 to 20 weeks; however, the fraction surviving at 36 weeks (about eight months) is remarkably consistent, i.e., about 20 percent, regardless of therapy (or the lack of it).1,2,6

The study reported in this issue by Hyde and associates (see page 603) from the Veterans Administration Lung Group appears to show a real advantage for treatment with doxorubicin (adriamycin) and cyclophosphamide in patients with extensive squamous lung cancer with both “well” and “poorly” differentiated histologic findings. There is a median survival of 24 to 25 weeks, with statistically significant superiority over the randomly allocated control group receiving cyclophosphamide only. Equally impressive is the projected survival of about 40 percent at 36 weeks (45 percent for “well” and 35 percent for “poorly” differentiated disease). Follow-up data on long-term survival will be eagerly anticipated in these patients; even assuming an exponential decline, it appears likely that 20 percent or more may survive for a year, which would be at least a twofold improvement over any results yet reported.

The skeptical physician dealing with thoracic diseases may yawn at this point and say, “So what? The patients are still dying of their cancer, and what real difference does a few weeks (or months) make?” My reply rests on two lines of evidence. First, progress in chemotherapy for cancer has followed a classic sequence: (1) identification of active single agents; (2) identification of active combinations of drugs; (3) impact on survival in a minority; (4) impact on survival in the majority; and (5) long-term survival, free of disease, in a substantial number of patients. We have now seen this sequence develop fully in acute leukemia, Hodgkin’s disease, histiocytic lymphoma, nonseminomatus testicular cancer, and regional small-cell cancer of the lung. In the more common “solid tumors,” such as cancer of the breast, colorectal cancer, and non-small-cell cancer of the lung, progress is somewhere between steps 2 and 4.

Secondly, experimental data on tumors support the concept that a relatively short gain in survival may correlate with a surprisingly great degree of killing of malignant cells; for instance, in the spontaneous AKR mouse lymphoma, chemotherapy with vincristine and prednisone produces a modest increase in life span, from 14 to 28 days, with practically no long-term survivors, and yet is associated with a 99.99 percent (4 log) reduction of clonogenic lymphoma cells in the thymus. There
is now clinical as well as experimental evidence that chemotherapy which is only capable of producing a "minor" impact on survival in advanced metastatic disease may have major influence on recurrence of tumor when used as a surgical adjuvant.\textsuperscript{13,14} Bonadonna and his group\textsuperscript{15} recently reported that patients with cancer of the breast and abnormal findings in the axillary nodes who receive cyclophosphamide, methotrexate and 5-fluorouracil after mastectomy have significantly superior survival at three years after surgery, compared to a randomized control group who received no adjuvant chemotherapy.\textsuperscript{15} Thus, combined therapy with doxorubicin (adriamycin) plus cyclophosphamide may prove much more successful in the setting of "minimal" residual disease after removal of primary squamous cancer of the lung. Validation of this hypothesis can be obtained only from large-scale, controlled clinical trials. Perhaps now some enthusiasm for these can be generated. In the meanwhile, those of us dealing with extensive disease will try to confirm the efficacy of this regimen and build on it toward something better.

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REFERENCES
1 Zelen M: Keynote address on biostatistics and data retrieval. Cancer Chemother Rep (part 3) 4:31-42, 1973

The Carotid Bodies Pathologic or Physiologic?

Dyspnea is the sensation of not being able to breathe enough to satisfy the ventilatory drive. It is probably the most common symptom in patients with diseases of the respiratory and cardiovascular systems. Patients have dyspnea either because of increased ventilatory drive or a limited ability to breathe.

Studies of a selected group of patients with a history of bronchial asthma who had had both of their carotid bodies removed demonstrate that the ventilatory drive in response to acute hypoxemia is lost.\textsuperscript{14} Wade et al\textsuperscript{8} demonstrated a similar absence of ventilatory response to hypoxemia in patients following carotid endarterectomy. Neither tidal volume nor respiratory rate was found to increase in response to acute hypoxemia in the absence of the carotid bodies. Thus, the carotid bodies appear to be the only organs that can directly stimulate ventilation in response to hypoxemia in man, in contrast to dogs and cats, in which the aortic bodies contribute some of the ventilatory drive in response to hypoxemia.\textsuperscript{4}

The carotid bodies of man have also been shown to be responsible for the increased ventilatory drive accompanying the metabolic acidosis of heavy exercise.\textsuperscript{5} The carotid bodies also appear to contribute to the ventilatory drive during the early period of exercise.\textsuperscript{5} Thus, in patients with impaired ability to breathe, resection of the carotid bodies can potentially reduce ventilatory stress.

That bilateral resection of the carotid bodies has more than a placebo effect on the ventilatory drive was simply demonstrated in the breath-holding studies of Davidson et al.\textsuperscript{6} Asthmatic subjects (selected on

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