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Perspectives and Commentaries

Pulmonary Function to Measure Response in Small Cell Lung Cancer

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SMALL cell anaplastic carcinoma of the lung (SCLC) is a unique clinical and pathological entity with a high labelling index and a rapid doubling time, both of which are expressed clinically by the short presentation period and early dissemination [1]. The vast majority of patients present with extrapulmonary disease involving mediastinal nodes or extrathoracic sites or both. The relatively central location of the tumors at diagnosis together with rapid growth generally result in obstructive pulmonic processes and early mediastinal metastases such that virtually all patients have technically unresectable disease. Pretreatment staging in this disease is therefore designed to elaborate and define the metastatic sites. To this extent those areas known to be frequently involved with tumor are routinely evaluated, including brain, liver, bone, bone marrow and other organs [2].

Staging and evaluation are, however, dynamic processes, with new staging methods being constantly proposed. For a procedure to be considered relevant to the staging and follow-up in SCLC it should either provide information which would potentially alter treatment, define areas of disease, define predictors of recurrence or allow for the early discovery of potential complications. Staging tests could be included as baseline evaluations for comparisons to subsequent tests or to define the evolution of disease. Recommended staging and prognostic factors have recently been reviewed by Osterlind *et al.* [3] as part of a workshop on SCLC. Other approaches have recently also found application, including the screening of marrow with soft agar cultures [4], the application of CT scans [5, 6] and the evolution of both definitions of disease and definitions of prognostic factors, as well as a myriad of biomarkers [7].

Multiple combination chemotherapy regimens have clearly shown the ability to produce dramatic responses, with complete response (CR) frequencies ranging as high as 65% in limited disease and with some long-term survivors [8]. Despite the high CR frequency, the majority of patients eventually have disease relapse or progression with subsequent demise secondary to disease. Therefore current staging techniques are not adequate to define those patients whose tumor reduction is suboptimal (i.e. with a higher probability of relapse). Further staging or re-evaluation methodology is urgently needed to help determine parameters which foreshadow relapse, thus allowing the oncologist to recommend new or subsequent treatment modalities to those patients with a higher probability of relapse.

Sørensen *et al.* [9] and Sorenson and Bake [10] have recently suggested that various pulmonary function tests may be yet another approach to the evaluation for response and prognostic factors for the patient with SCLC. These studies have attempted to utilize various pulmonary function tests as a means of assessing complete response adequacy as well as determining their value for prognosis. One must ask, however, whether the use of sequential pulmonary function studies, based on the available data, can serve as such an assessment.

Based on a review of some currently available material [11-16], as well as the reports by Sørensen *et al.* [9] and Sorenson and Bake [10], one must conclude that it is premature to advocate ventilation perfusion scanning or other pul-

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monary function tests for staging or follow-up in small cell carcinoma. These tests are both expensive and non-specific. For example, bronchospasm, obesity, pulmonary emboli, tumor emboli and atelectasis (seen with bed rest) can all alter ventilation-perfusion relationships in the lung. Therefore the discovery of changes would have to be explained by eliminating these factors. In addition, the appearance of new deficits would not be specific for tumor. Furthermore, ventilation-perfusion relationships can dramatically change because of tumor regression, or may not change because of scar formation, even in the face of complete response. Finally, there may be variable change in association with reperfusion injury.

Since patients with small cell carcinoma of the lung are frequently heavy smokers with a median age of approximately 60 yr, it would be anticipated that the majority of these patients would have at least some evidence of chronic obstructive pulmonary disease (COPD). Baseline studies prior to the evolution of SCLC in these individuals are usually not available, so that 'significant' improvements in pulmonary function tests after treatment may be a simple reflection of decreased tumor bulk and the slight opening of mainstem bronchial airways, and not necessarily a reflection of the degree or nature of the response.

Many of the tests utilized in pulmonary function assessment, such as FEV_1, PF, RV and TLC, are all effort-dependent studies and changes herein may be non-specific and a reflection of the patient's greater sense of well being, improved performance status or both. Change in effort activity was at least partially responsible for the changes in some of the PFTs since the forced expiratory flow (FEF_{50}) (at 50% vital capacity), the most effort-independent of all the tests utilized, did not change.

Diffusion capacity was another parameter studied and (perhaps) showed no significant change. However, there was a large standard deviation and one needs to correct the diffusion capacity for alveolar volume (reflected by total lung capacity), which could result in a decrease of the diffusion capacity after treatment. Indeed, many chemotherapeutic agents (e.g. methotrexate) are known to decrease diffusion capacity. On the other hand, if total perfusion of the lung were to increase because of regression of tumor, one would expect the diffusion capacity to increase or at least remain stable.

Ventilation-perfusion scanning as a method of assessing response to chemotherapy was also used in these studies and is a particular concern as a parameter of measure because of the technical problems, the expense and the wide standard deviations. This is one of the most difficult tests to apply for serial assessments.

If one were to utilize a serial assessment of pulmonary functions, effort independent variables would be important and should include FEF_{50} and diffusion capacity. However, one would also need to define the inherent variability of their pulmonary fuction by repeated measurements as well as control for smoking cessation, sense of well being (especially in effort dependent variable), training effects and technical expectations, all of which may encourage the patient to improve performance at serial sessions. In addition, because either the disease (e.g. Eaton-Lambert syndrome) or effects of chemotherapy (e.g. vincristine toxicities) can occasionally result in weakness, effort-independent variables may also produce inadequate data. In addition, one should get a history which reflects recent activities of the patient, including an assessment of the potential underlying chronic COPD. For the most part, closing volumes will be elevated and extended periods of inactivity may produce varying degrees of atelectasis which might be reflected in decreased lung compliance, which in turn may independently affect the pulmonary functions as well as the pulmonary perfusion scans. Finally, one would need to know and record the concurrent medications as many of these (beta agonists, theophyllines, etc.) may affect pulmonary function tests.

In order to introduce a series of tests as part of the sequential analysis of patients with SCLC, it would first be necessary that sufficient numbers of patients be evaluated with the test in order to draw valid correlations with the index to be measured. For example, in order to assess differences in survival according to subgroups large numbers are necessary, or else one does not have sufficient power to detect even magnitudes of difference. Secondly, it is not surprising that patients with central lesions and obstructive processes should have many of their obstructive problems resolved with some degree of tumor regression. Whether the degree of pulmonary function improvement correlates with the degree of response must be indexed against all patients, not just complete responders, in order to see if there are any linear relationships with improvement. Finally, in order to ask the appropriate application of pulmonary function tests one would have to know both the sensitivity and specificity of the test in determining that index which one seeks, e.g. its predictive capacity for determining early relapse or changing therapeutic options.

From the foregoing it becomes clear that a large number of patients with small cell carcinoma of

the lung will need to be screened and followed sequentially in order to determine if there be merit to the routine application of pulmonary function testing in this disease. Based on the cost and effort associated with pulmonary function tests, they are unlikely to produce information which will either alter therapy, define areas of disease or define the predictors of recurrence. This would raise serious questions regarding the cost benefit of further study of this approach. There remains, however, the possibility that pulmonary function tests may yet be useful in defining complications of therapy as they evolve. In particular, several studies are now suggesting that there may be potential utility to the application of adjuvant radiotherapy to chemotherapy in patients with limited disease SCLC. As systemic therapy becomes more effective (increased number of long-term disease free survivors) it will be necessary to again evaluate the role of adjuvant irradiation and one may need to define the degree of pulmonary compromise induced by chest irradiation in that light.

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