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Perspectives and Commentaries

Prognostic Factors for Small Cell Carcinoma of the Lung

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(A COMMENT ON: Vincent MD, Ashley SE, Smith IE. Prognostic factors in small cell lung cancer: a simple prognostic index is better than conventional staging. *Eur J Cancer Clin Oncol* 1987, **23**, 1589–1599.)

A FIVE YEAR survival rate of 5–10% in patients with small cell carcinoma of the lung (SCCL) has not been altered significantly during the past decade despite notable achievements in the development of active chemotherapy regimens and progress in the understanding of the biology of the disease. A central dogma of clinical strategies has been to fashion treatment protocols on the basis of a staging system which allocates patients into those with disease confined to one hemithorax (limited disease) versus those with disease beyond such confines (extensive disease). This approach has entailed meticulous clinical status evaluations, assessment of hematological and serological parameters, invasive diagnostic procedures and interpretations of diverse forms of radiological scanning. Concurrently and intertwined with staging procedures it has been the goal of investigators to identify and assess predictors of the natural history of SCCL. The major prognostic factors most consistently identified to date have included extent of disease and clinical performance status. The median survival of patients with limited stage disease ranges from 10 to 15 months and for those with extensive disease from 7 to 11 months. Similar relative survival differences are predictable by knowledge of performance status. More recent (valuable) prognostic attributes have included those that attempt to quantitate tumor size both locally (mediastinal involvement) [1] or systemically (sites of metastatic spread) [2]. A number of other prognostic variables have been studied including the value of serological markers such as the carcinoembryonic antigen (CEA) [3], lactate dehydrogenase (LDH) [4] and alkaline phosphatase (AP) [5]—in themselves viewed by some to correlate in part with tumor bulk [3, 5]. Although these and numerous other significant prognostic attributes have been identified their synergistic impact has unfortunately not been realized satisfactorily. This omission, we argue, may be the result of a lack of appropriate statistical methodology rather than neglect.

Notwithstanding, such an assertion has implications pertaining to a more meaningful staging system, as it is becoming increasingly apparent that the current staging system lacks stringency and may not in fact reflect tumor burden accurately. Noteworthy in this respect has been the demonstration that a select group of patients with limited disease, those with the absence of mediastinal involvement [1], manifest a favorable survival potential relative to others within the category. Similarly, the number of metastatic organ sites in patients with extensive disease predicts for survival differences [2]. Clearly, the amalgamation of patients into either disease category under the current system enshrines prognostic biases which may have deleterious bearings on treatment planning approaches and on the interpretation of responses to treatment.

In an attempt to resolve these dilemmas, Vincent *et al.* have addressed this issue in a recent article in the journal [6]. The aim of the British study was to assess the importance of currently

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available prognostic attributes of patients with SCCL with both univariate and multivariate approaches, and to propose new staging strategies based on such analysis. The study first identified, and ranked by importance, all significant prognostic factors accumulated on patients who were enrolled in various clinical trials over a 10-year interval. Select attributes were identified that retained independent prognostic significance following multivariate analysis that employed a proportional hazards model. These select factors were used to propose alternatives to the current staging system for patients with SCCL. One model utilized serum albumin, performance status and alanine transaminase to devise a stratification scheme composed of three groups which were felt to represent patient prognosis more precisely and reflect tumor burden more accurately. This important study, however, did not single out one particular prognostic model for general use and proposed that the concept should be further explored. The crux of the study, however, may suffer from limited available statistical methodology.

In an attempt to resolve this problem, we have proposed a more definitive model based on the utilization of a novel statistical methodology which employs the technique of recursive partitioning and amalgamation algorithms (RECPAM)—two clustering methods well suited for obtaining strata. A distinct advantage of the methodology derives from its emphasis on the assessment of interactions among prognostic variables, an attribute which is not well exploited by predictive models based on stepwise logistic or Cox regression analysis [7]. Using the RECPAM approach we evaluated 35 pretreatment attributes in 635 patients with SCCL [8]. The process identified five distinct prognostic groups defined in a binary decision tree paradigm by the following attributes: disease extent, performance status, mediastinal involvement, serum alkaline phosphatase, sex and age. The five groups were distinguished by median survival times of 59, 54, 46, 35 and 24 weeks, respectively. It was clear that, in fact, the approach defined prognostic strata that defy conventional staging barriers such that subpopulations of patients from both the limited and extensive stage categories assume similar prognosis. Wider methodological applicability allowed for analysis of interactions among select prognostic attributes such as biological markers and extent of disease [9].

The momentum imparted by the current multivariate approaches should set the stage for universal consensus on the most advantageous application of prognostic factors in patients with SCCL. It is hoped that this aim would enable a standardized approach to patient stratification, would strive for more rational allocation of patients into treatment protocols and, furthermore, remove prognostic biases from interpretation of clinical trial results.

Foremost in the realization of such a goal should be the attainment of agreement on the choice and definitions of prognostic variables (allocated into any stratification scheme). Current differences in the choice and evaluation of prognostic factors, including the definition of extent of disease, stem from inherent intercenter biases, population sample differences, the influence of other concurrent diseases and variability in the automated analysis of serological markers or other laboratory parameters.

It is conceivable that construction of a RECPAM multicenter stratification scheme would facilitate patient management in at least three primary respects. Firstly, the methodology may be superior to presently available methods of stratification since it enables physicians to enter patients directly into a stratification scheme in clinical settings and simultaneously attain a prognostic score on individual patients. Secondly, more rational patient allocation into clinical trials could be employed with the identification of distinct prognostic groupings most suited to benefit from specific treatment modalities; for example the role of surgery could be explored more realistically in patients with favorable limited disease. Finally, a further goal of this type of research as suggested by Vincent *et al.* [6] would be to seek a compromise model which would serve the mutual interest of both cost effectiveness and minimization of patient risk and discomfort from invasive staging procedures, and yet retain a true reflection of disease extent and hence tumor burden. Again, this aim may be achieved by uncovering correlations between laboratory parameters which are relatively inexpensive and more costly and invasive staging procedures, and subsequently substituting the former for the latter in a prognostic scheme. For example it has been shown by some groups [1, 10], that assessment of the serological marker lactate dehydrogenase correlates accurately with bone marrow metastasis in SCLC.

In conclusion, given the foregoing assertions, it is clear that there are a number of ways to achieve similar stratification schemes and that one should seek to exploit the utilization of simple, non-invasive and least costly parameters in a new staging system. Ultimately it is hoped that a standardized approach would be adopted universally by consensus.

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