Stage Classification and Prediction of Prognosis

Difference between Accountants and Speculators

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Stage classification and predicting prognosis are integral facets of cancer care. Clinicians often lament that the stage classification system falls short in predicting prognosis, and suggest that the classification system should include other prognostic factors. It is germane to explore these issues because work on revisions of the stage classification system are currently underway. This article reflects on the nature of classification and prognostication to contribute to our collective thinking.

THE TASK OF THE BEAN COUNTER

"Make everything as simple as possible, but not simpler," Albert Einstein

The Nature of Classification

What is stage classification? Fundamentally, it is a description of the anatomic extent of a cancer, involving clear definitions to consistently categorize a patient's tumor. Stage classification is inherently concrete, designed to apply to an individual, and to consistently produce the same stage assignment, given the same staging information.

Nevertheless, change is constant. New imaging and biopsy procedures add to the available information but do not affect the definition of tumor, node, metastasis (TNM) classes or stages. More importantly, more data uncover nuances leading to greater complexity. Periodic revision of stage classification system is needed. However, the importance of consistency dictates that changes occur only occasionally in a well defined, formal manner.

Stage classification is like the work of an accountant, who reviews an individual business's financial records. Transactions are assigned to particular categories, which must be consistent and universally accepted. As new types of transactions are developed, new standards are defined periodically, maintaining universal consistency.

Other classifications also apply (e.g., histologic type, genetic mutations, or the patient's performance status). However, although these are useful, they do not per se affect the anatomic extent of disease. Similarly, other accounting classifications (e.g., a bond rating) are important, but do not alter where a specific transaction is placed on the financial balance sheet.

Uses of a Stage Classification System

Primarily, stage classification provides a consistent means of communication, allowing us to speak clearly to one another about an individual tumor or a group of tumors. The anatomic extent of disease is also a major factor affecting prognosis, but prognosis is affected by many other factors (e.g., the treatment given, tumor type, comorbidities).

The anatomic extent of disease is helpful in selecting a treatment approach, along with other factors (e.g., comorbidities, logistics, and patients' preferences). However, the role of a particular treatment is defined by data from clinical trials; the stage classification only provides an ability to communicate and apply a clinical trial's results.

How Should we Define Stage Classification?

Where should we draw the lines between TNM classes and stage groups? Initial definitions were largely empiric, but we need a system that can be applied consistently. Ideally, we should segregate tumors into groups with similar biologic behavior; patients in these groups would likely remain coherent even as treatments evolve, and the prognosis changes. But how do we define biologic behavior? Can this be determined by the anatomic extent at diagnosis? Is the biologic behavior relatively stable over time, or does this evolve (e.g., from indolent, to locally invasive, to capable of metastasizing)? Unfortunately, we have little knowledge to guide us in answering these questions.

Should we abandon anatomic features, and define tumor biology from genetic characteristics? Our understanding of how genetic changes influence biologic behavior is rudimentary, centered primarily on specific mutations that predict response to a particular targeted treatment. We know little about how genetic changes affect actual biologic behavior over the course of the disease. The recent study, showing that acquired resistance of lung cancers to an epidermal growth factor receptor inhibitor is because of transformation of adenocarcinoma into small-cell lung cancer in a substantial proportion of patients, should make us realize how little we really know about tumor biology.[1]

Only natural history (observation without any active treatment) allows actual assessment of tumor biology; this

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is available in only a few patients (with severe comorbidities), who are not representative of the general population of patients. Actual natural history studies are not ethical and are therefore unattainable.

Can the prognosis of patients in general (who are being treated in various ways) serve as a surrogate for natural history and provide clues about biologic behavior? This approach was used in recent revisions of the stage classification system. However, in the International Association for the Study of Lung Cancer database, the 5-year survival of patients with the same anatomic extent of disease, varied markedly depending on geographic region, type of source data, and other factors, likely reflecting that the observed prognosis is perhaps determined less by the inherent tumor biology than factors, such as the treatment given and the effectiveness thereof, socioeconomic factors, and comorbidities. This problem was addressed (indirectly) during the development of the 7th edition of the lung cancer stage classification by requiring that TNM classes and stage groups be separated not by their *actual* prognosis (which was highly variable), but by *differences in prognosis* that were consistent within multiple subgroup analyses (regions, histologic type, clinical/pathologic etc.).[2] Unfortunately, this approach doesn't actually eliminate or correct for confounding factors. Thus, observed outcomes reflect many factors (primarily not related to the anatomic disease extent), and should not be confused with the natural history of the disease.

SPECULATORS, GAMBLERS, AND FORTUNE TELLERS

"It is difficult to make predictions, especially about the future."

Winston Churchill

Once cancer is diagnosed, we immediately want to predict the prognosis. This is undeniably a major clinical need. In developing ways to do this, it is helpful to reflect on the fundamental nature of this process.

Prediction of prognosis is inherently multifactorial and complex (Fig. 1). Cancer often becomes a dominant issue affecting lifespan, but there are still many things at play (e.g., disease extent, comorbidities, and treatment decisions). Furthermore, the role various factors play depends on the situation. A particular comorbidity may have an impact for one particular treatment but not for another. A mutation may be critical for treatment with a targeted agent, but have little importance otherwise.

Prognostication is inherently associated with a degree of uncertainty. The future is impacted by many factors in a complex manner, including unpredictable random new events. The number of prognostic factors we have not yet identified likely far exceeds those we know about. We have focused on expressing what we know, but we need tools to describe the uncertainty of the prediction, and to what extent outcomes are determined by known prognostic factors versus unknown factors.

Prognostic data fundamentally apply to a population of patients. In a large population, other known and unknown factors will likely approach a general mean and be similar to the

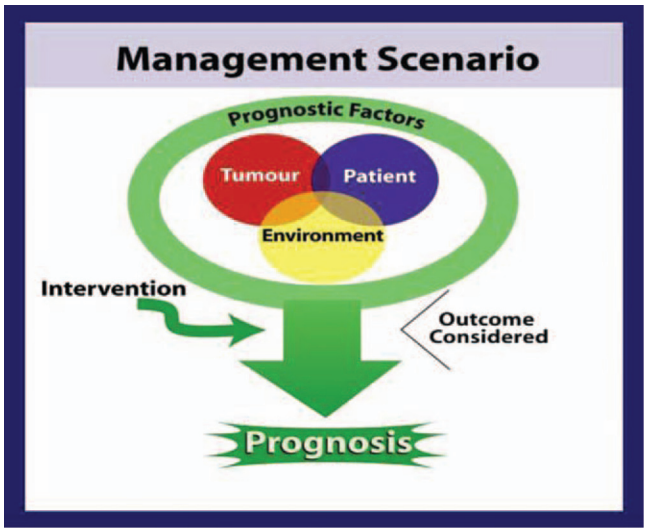

FIGURE 1. Classification of prognostic factors from Gospodarowicz et al.[3]

population the prognostic model is derived from. However, we want to predict prognosis for an individual patient. At least theoretically, one might be able to predict individual prognosis by including enough factors, but this is inherently associated with ever greater uncertainty. At the level of an individual, a personalized prediction of prognosis would likely be associated with such a wide confidence interval that the prediction is of little use.

Prognostication is also an inherently fluid process. As soon as an estimate of prognosis is available, clinicians start trying to improve the outcome. Thus, the estimate of prognosis for a specific individual will likely be different 2 years from now, than it is for the same individual today. Furthermore, this specific individual's prognosis changes as the course of the disease and treatment unfold and other events occur.

Prognostication is inherently prone to biases and self-fulfilling prophecies. If we are convinced of a grim outlook and only institute end-of-life measures, we may never realize what the outlook would be if treatment was given.

Thus, prognostication is quite different than stage classification. It is complex and dependent on multiple factors, including many that are unknown or unpredictable. It is fluid, constantly changing, and inherently associated with uncertainly. It is designed to apply to a population of patients, which is not how we want to use it. Prognosis cannot be defined at intervals by a carefully worded document, which establishes a standard; it is inherently a guess about the future.

The activity of prognostication is much more akin to that of a speculator or gambler. It involves the future, which is inherently somewhat unpredictable. It is fluid, affected by many factors, analogous to interest rates, supply and demand, or the opponents one is facing at the poker table. It is constantly evolving, much like a stock speculator affected by market fluctuations, or a gambler by each card played.

DISCUSSION

Classification and prognostication are inherently different. Keeping these separate maximizes the effectiveness

of each. Stage classification must be consistent and can be updated periodically. Prediction of prognosis is complex, multifactorial, and is constantly changing.

Stage classification should describe the anatomic extent of disease only. Other classifications and characteristics of the patient and tumor are important, but mixing these together makes the system overly complex, and only obscures much of what each classification can provide.

It is reasonable to use prognosis (even better consistent differences in prognosis among various subgroups) to determine how to separate TNM classes and stage groups. However, prognosis is not providing insight into the tumor biology. It is highly confounded, perhaps, mostly by the treatment given. Accounting for treatment provides a slightly better assessment (e.g., pathologic stage after R0 resection), but still leaves many factors unaddressed. Furthermore, stage classification must be practical; overemphasis of (confounded) statistical findings risks making the system too illogical and difficult to use.

A system to determine prognosis is clearly needed. This should present what is known and how much of the outcome is unexplained by known prognostic factors. It should also depict the degree of uncertainly, especially when applied to individual patients. The system should be reasonably validated, yet flexible enough to accommodate emerging new factors.

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