Re: Colon Cancer Survival Rates With the New American Joint Committee on Cancer Sixth Edition Staging

O'Connell et al. *(1)* showed that the stage groupings in the newer sixth edition of the tumor-lymph node-metastasis (TNM) staging system more distinctly stratify survival than the fifth edition *(2,3)*. However, survival was worse with T4N0M0 (stage IIB) than with T1-2N1M0 (stage IIIA) disease. Review of 351 000 colon cancer case records in the National Cancer Data Base confirms this finding (A. Stewart, personal communication). In the accompanying editorial, Burke *(4)* states that this breaks a fundamental rule of the TNM staging system—that survival should decrease with increasing stage grouping. On this basis, he recommends the American Joint Committee on Cancer (AJCC) revert to the fifth edition of TNM staging for colon cancer staging.

In most cases, survival usually decreases with each higher stage group. However, stage group primarily reflects increasing anatomic extent of disease. For colon cancer, stage II is local disease with negative lymph nodes and stage III denotes positive lymph nodes. The recognition that T4N0 tumors had a worse prognosis than T3N0 was the basis for dividing stage II of the fifth edition into stages IIA and IIB in the sixth edition. The findings of O'Connell et al. support this division and do not require that we abandon this improved disease classification.

Burke also raises more fundamental questions regarding TNM: that it fails to account for the prognostic impact of response to presurgical therapy and does not allow for use of nonanatomic biologic factors. Further, he states that the TNM system that assigns cases to stage groups, or "bins," should be replaced by programs that quantify prognosis for an individual.

Grouping patients with similar disease is necessary for assessing the impact of treatments in similar patients and for population surveillance of cancer incidence and outcome. However, this procedure does not preclude the use of any factors that affect cancer prognosis or the future reorganization of groups around such factors. It is everyone's hope that advancing science will fundamentally change understanding of cancer prognosis. The challenge is to identify those factors that are sufficiently robust that they can be reliably measured and applied to all cases.

Toward this goal, the AJCC examined nonanatomic factors and alternate staging schemas for the sixth edition revisions of the TNM staging system. International workshops addressed the use of neural networks and nonanatomic prognostic factors, with concrete recommendations used in revising TNM staging *(5)*. The International Union Against Cancer (UICC) also published a monograph, now in its second edition, that discusses both the methodology for assessing prognostic factors and specific factors at each anatomic site of cancer and includes a chapter on the use of neural networks *(6,7)*.

Another advance to allow the use of new prognostic factors, developed by the AJCC in collaboration with the other cancer surveillance organizations, is the Collaborative Staging System, a standardized data collection platform for cancer staging being implemented across North America by all hospital and population registries (http://www.cancerstaging.org). A key component is that it includes fields for collection of disease—specific non-anatomic factors that may affect prognosis.

Staging with presurgical therapy is based on physical examination and imaging studies. For population surveillance and examination of overall benefits from therapy, the extent of cancer at the time of diagnosis is the critical issue. However, response to treatment may

provide useful prognostic information. Similarly, comorbidity affects outcome. Future prognostic algorithms and cancer data systems will certainly include such information.

The AJCC and UICC disagree that the TNM staging system should revert to the fifth edition staging system for colon cancer. We agree that the TNM staging system should undergo continuous scrutiny and periodic revision to give patients and doctors the best possible information and to provide a basis for study of the societal impact of improvements in cancer prevention, diagnosis, and treatment.

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Notes

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RESPONSES

In our recent article *(1)* that reported the 5-year survival rates for colon cancer by use of the newly updated American Joint Committee on Cancer (AJCC) sixth edition staging system, we were surprised to find that colon cancer survival was worse for T4N0M0 (stage IIB) than for T1-2N1M0 (stage IIIA) disease. This finding initiated some discussion as to whether or not we should revert back to the fifth edition staging system *(2)*—with the above editorial providing some background and additional information regarding current issues pertaining to staging systems development. Our sentiment, and response to the editorial and correspondence by Edge et al., is that the sixth edition staging system clearly allows for increased stratification of the disease much more than the prior fifth edition. The gaps in survival curves between stages II and III of the fifth edition were probably too large and thus justify the increased number of substages in the sixth edition. It is really because of the increased detail provided by the sixth edition that we were able to identify the survival differences between the more advanced stage II patients and the early stage III patients. Such detail is also good because it will likely allow us to develop increasingly focused clinical trials. As an example, we have received much feedback from our study saying that the stage IIB survival rate is lower because of the lack of adjuvant therapy. As such, this cohort may need to be studied in a trial to validate this observation.

Although we agree that we should not revert to the fifth edition, we also agree with Edge et al. that there are several issues to address currently regarding the staging of colorectal cancer. The use of molecular markers or a panel of items has shown promise in studies *(3)* and may be an important addition in the future to staging systems. Also, the inclusion of some sort of comorbidity risk adjustment is an important issue to address—for the study of receipt of therapy, quality of care, and also survival outcomes. Finally, the issue of staging rectal cancers has become increasingly complex with the advent of neoadjuvant therapy, and the staging system for rectal cancer needs to have thoughtful improvements made. Although our original study addressed only colon cancer, we attempted to perform this same analysis with rectal cancer. We came upon several issues that made the analysis difficult to perform—most notably the lack of reliable pretreatment clinical-staging information. In the cancer registry, we have the pathological stage after surgical resection. However, this stage may not be the most appropriate for prognosticating outcomes, as poignantly exemplified by the number of cases with a complete response *(4)*. In any case, if we are to use cancer registry data to help study survival rates for rectal cancer patients, more data variables will probably be needed.

In summary, and as concluded in the above editorial by Burke**,** continuous scrutiny and thoughtful revision of the colorectal cancer staging system are needed.

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The leadership of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) raise three issues in defense of their TNM staging system: 1) the staging system should be used even when the stages are

disconnected from prognosis, i.e., when increasing stage is not associated with increasing mortality (outcome crossover), 2) new biomarkers can be added to the TNM stages, and 3) the TNM stages can reflect the effects of new therapies on prognosis.

For the sixth edition of the staging manual, stage II was divided into two substages (IIA and IIB), where stage IIA had a better survival than stage IIB. But the survival of the stage IIB patients was worse than that of the stage IIIA patients, which led to a crossover of the outcomes of stage IIB patients with those of stage IIIA patients. The AJCC and UICC leaders defend the sixth edition's outcome crossover by stating that the TNM stages must reflect increasing anatomic extent of disease and not necessarily increasing mortality. They state that, because the sixth edition's stages maintain an increasing anatomic extent of disease, it should be used, even if the increase in the stages does not represent an increased disease-specific mortality.

Anatomic extent of disease is preeminent in the TNM staging system because of the AJCC and UICC's belief in the contiguous spread of disease model, where spread is indexed by detection of the largest tumor (T), affected regional lymph nodes (N), and distant metastases (M), which are the TNM variables. Even if the contiguous spread model were correct, there is no necessary reason why the TNM stages should perfectly correlate with the anatomic extent of disease, especially because the TNM variables are not equally easy to detect. Further, the TNM variables track time but not in equal time intervals. Thus, tumor size in centimeters reflects a different rate of tumor time than the number of involved lymph nodes, and both reflect a different rate of time than metastases. Finally, a therapy may differentially affect patients categorized by the TNM stages. If, for example, a new therapy affects the outcomes of patients with lymph node involvement more than that of patients with large tumors, then the TNM staging system can exhibit outcome crossover. In fact, the inability of the TNM staging system to take a new therapy into account may have caused the current crossover problem.

The originators of the TNM staging system avoided the inaccuracy inherent in the TNM variables by not substratifying beyond the ability of the TNM variables to index disease outcome, thus maintaining the relationship between stage and prognosis and avoiding outcome crossover. Now, for the first time in the history of the TNM staging system manual, in the sixth edition, the stages that are based on extent of disease do not track with death due to disease, and the AJCC and UICC chooses to be guided by extent of disease instead of prognosis.

Although the leaders, in their defense, state that new prognostic factors can be added to the staging system and new therapies can be taken into account, it has been 12 years since the addition of new biomarkers and the creation of a computer-based prognostic system were first proposed *(1)*. Yet neither of these ideas has been acted upon. For several decades, estrogen and progesterone receptor status, and more recently HER2 status, has been used to assess the prognosis of, and make therapeutic decisions for, women with breast cancer. Why have they not been integrated into the TNM staging system? It is because one cannot add biomarkers to the TNM staging system; adding biomarkers requires an increase from 40 outcome bins to hundreds if not thousands of outcome bins, resulting in a complexity that would only lead to clinical confusion. A more fundamental reason why is the AJCC and UICC's dogma of the supremacy of the anatomic extent of disease, as indexed by the TNM variables, over prognosis. New molecular biomarkers predict outcome, and they need not have any relationship to anatomic extent of disease but rather, they may correlate with the biology of the disease itself. It is not clear how molecular biomarkers that are based on outcome can be integrated within the TNM stages when the stages need not be related to outcome.

The TNM staging system was designed to provide outcomes for patient who received only surgery. Because therapy affects outcome, how can such a system predict outcomes for patients who also receive neoadjuvant and/or adjuvant therapy, how can it provide outcomes for therapies given that are based on molecular biomarkers rather than TNM stage, and how can it provide outcomes for patients who have prognostic biomarkers that are not represented in any TNM stage? Further, it is not clear how patients can be stratified by therapy in the TNM stages or how the TNM staging system will deal with combinations of therapies. In essence, how does a crude classification system that is based on anatomic extent of disease system cope with personalized medicine, where every patient has a potentially unique set of biomarkers and an individual prognosis?

In the end, the issue of whether the TNM staging system should revert to the fifth edition may be moot because medicine is leaving the domain of anatomic extent of disease and entering the domain of biological determinism and computer-based prognostic systems for personalized medicine. The Committee for Molecular Biomarkers in Medicine (http://www.cmbm.net) is currently working toward these goals.

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