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

Stages II and III of the newly revised tumor-node-metastasis staging system for colon cancer (American Joint Committee on Cancer [AJCC] Staging Manual sixth edition) differ from those in the fifth edition *(1)*. In the sixth edition, stage II is subdivided into IIa (T3N0) and IIb (T4N0) and stage III is subdivided into IIIa (T1–2N1M0), IIIb (T3–4N1M0), and IIIc (anyTN2M0). This stratified grouping was motivated by the large difference in survival between stage II and III patients noted in the analysis of the National Cancer Data Base registry by Greene et al. *(2)* and recognition that having a T4 tumor could have a greater impact on prognosis than regional lymph node involvement *(3)*.

Recently, O'Connell et al. *(4)* reported survival of 119 363 colon cancer patients from the Surveillance, Epidemiology, and End Results (SEER) program and demonstrated that survival was worse for the subset of patients with stage IIb (T4N0M0) than for those with stage IIIa (T1–2N1M0) tumors. The authors attributed this paradoxical survival difference to several potential factors: 1) preferential administration of chemotherapy for stage IIIa patients; 2) understaging of T4N1 tumors as T4N0, thereby resulting in migration of aggressive disease from stage IIIb to stage IIb; 3) greater likelihood of a curative en bloc surgical resection for stage IIIa; and 4) a relative disproportional increase of biologically more aggressive tumors in stage IIb. However, because the SEER

Table 1. Five-year survival by AJCC sixth edition stages IIb and IIIa*

Group of patients	Stage IIb	Stage IIIa	*P* value†
Overall			
No. of patients	117	82	
5-year DSS,‡ %	89.0	94.1	.21
5-year DFS,§ %	53.7	66.0	.12
Chemotherapy group			
No. of patients	52	68	
5-year DSS,‡ %	85.3	96.3	.07
5-year DFS,§ %	43.8	68.3	.02
Nonchemotherapy group			
No. of patients	65	14	
5-year DSS,‡ %	91.6	83.9	.58
5-year DFS,§ %	61.2	55.6	.72

*AJCC = American Joint Committee on Cancer.
†*P* value was from a two-sided log-rank test comparing stages IIb and IIIa.
‡Five-year disease-specific survival rate.
§Five-year disease-free survival rate.

program does not contain information on chemotherapy or the extent of resection (R0 versus R1 versus R2), the authors were unable to fully explain this paradox.

Using the Memorial Sloan-Kettering Cancer Center (MSKCC) Tumor Registry Database, we identified patients who had undergone resection of a primary invasive colon adenocarcinoma and for whom at least 3 years of follow-up were available. From this group, we identified 117 stage IIb and 82 stage IIIa patients with colon adenocarcinoma who had undergone a curative resection in whom detailed information on adjuvant chemotherapy was available. Median follow-up for these two groups was 57 months, and median ages were 66 years (range = 31–93) and 62 years (range = 31–91) for stage IIb and stage IIIa, respectively.

As O'Connell et al. had predicted, patients with stage IIIa tumors received adjuvant chemotherapy more frequently than patients with stage IIb tumors (83% versus 44%, $P<.001$). We noted that overall, 5-year disease-specific survival (DSS) and 5-year disease-free survival (DFS) in our study were superior for patients with stage IIIA tumors compared with those with IIB tumors, although these differences did not reach statistical significance (Table 1). For the subset of patients who received chemotherapy, those with stage IIIa tumors had a statistically significant improved DFS relative to those with stage IIb tumors. In contrast, for the subset of patients who did not receive adjuvant therapy, earlier stage did indeed correspond to superior prognosis (Table 1).

Our analysis has several limitations that deserve mention. First, our findings may not be generalizable because all surgery was performed at a single, specialized cancer center. This drawback is outweighed by the advantage of having accurate information about adjuvant treatment and survival outcomes in addition to staging. In addition, insofar as our data were retrospectively collected and analyzed, it is possible that selection bias for and/or against adjuvant therapy influenced our results.

Burke recommended in his editorial that until the advent of a revised edition, clinicians and researchers should rely on the earlier fifth edition of the AJCC Staging Manual for colon cancer *(5)*. We agree that the paradoxical survival difference is a definite concern for the sixth edition, as survival should decrease with advancing stages. However, our data suggest that this paradox may be based on a heterogenously treated study population.

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Notes

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RESPONSES

High-quality cancer registries such as the Surveillance, Epidemiology, and End Results (SEER) program are extremely useful for hypothesis generation and, hopefully, will lead to future studies that include data with a greater degree of clinical detail. Such studies may include randomized prospective clinical trials or highly detailed retrospective studies like that presented by Jeong et al.

The American Joint Committee on Cancer sixth edition staging for colon cancer makes excellent theoretical sense and was based on well-performed analyses *(1)*. Thus, our finding was somewhat surprising that stage IIb cancers had lower survival than IIIa when we examined the staging system by using the SEER program data (although these results were largely confirmed by analyses that used another high-quality cancer registry, the National Cancer Data Base) *(2)*. In our article, we discussed some possible reasons for why this paradoxical finding occurred *(3)*, but because SEER does not have the appropriate data to address these issues, there remained unanswered questions that help set the stage for further work to be performed.

In this regard, Jeong et al. have importantly taken the next step with their data. Their analysis are meaningful because they were able to compare outcomes for patients with stage IIb and IIIa disease, as well as separate outcomes for those who received chemotherapy and those who did not. Their conclusion was that a

heterogeneously treated population is at least in part responsible for the paradoxical finding regarding survival for these stage groups. Although we agree with this conclusion, there are still "paradoxical" results in their data that lead to additional questions. For example, among patients treated with chemotherapy, why do patients with stage IIIa disease appear to do better than patients with stage IIb disease? This result is consistent with our findings, and it admittedly remains puzzling. Also, in their analysis, the patients with stage IIb disease who received chemotherapy appear to have lower survival than the patients with stage IIb disease who did not receive chemotherapy. Is this a result of selection bias—i.e., were the patients at higher risk (e.g., because of obstruction or perforation)—or could stage migration still be at play so that T4N0 disease was in fact T4N1 disease? If we believe and adhere to the guidelines from the American Society for Clinical Oncology that require 12 lymph nodes to be examined, were an adequate number of nodes removed from these patients? Baxter et al. *(4)* reported that the median number of lymph nodes retrieved at the population level for a colon cancer resection obtained from the SEER database was nine.

In the big picture, the analyses by Jeong et al. should be appreciated in that they used their own data, which contain more appropriate clinical data than the SEER database, to address the hypotheses generated by the population-based cancer registry analyses. More quality studies, such as this one by Jeong et al., need to be performed, perhaps that include examination of the molecular components of the tumors, to explain the paradox. If further study is needed, a clinical trial should then be designed.

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The American Joint Committee on Cancer and the International Union Against Cancer correctly state that the TNM staging system is an anatomic-extent-of-disease-at-detection system and that it need not have any clinical relevance in terms of patient outcome *(1)*. However, most clinicians still believe that there is a direct connection between anatomic-extent-of-disease-at-detection and patient outcome, and they persist in using the TNM staging system, as if each step up in anatomic stage was associated with a step down in prognosis.

Recently, it has become difficult for clinicians to use the TNM staging system because it does not integrate important prognostic biomarkers, for example, in breast cancer, grade, receptor status, and gene and protein biomarkers. How can the TNM staging system assist in the selection of radiation therapy, hormonal therapy, chemotherapy, or molecular therapy if it cannot accommodate tumor grade, estrogen receptor and progesterone receptor status, and HER2 expression?

The TNM staging system's exclusion of nonsurgical therapies can produce unexpected results. For example, patients in a higher stage who receive a nonsurgical therapy that was not offered patients in a lower stage can have a better prognosis than those in the lower stage; i.e., there can be outcome crossover *(2,3)*. Thus, Jeong et al. *(4)* found that the outcome crossover between stages IIb and IIIa in colorectal cancer was due to patients receiving a therapy not recognized by the TNM staging system.

If all a clinician wishes the TNM staging system to do is provide anatomic-extent-of-disease-at-detection information without regard to prognosis, then the current situation is tolerable, but clinically uninformative. Clinicians are recognizing the inadequacy of the TNM stages and are providing therapy that is based on prognostic biomarkers related to individual patients and specific therapies. The TNM staging system is losing its clinical relevance because it no longer informs prognosis or drives therapy.

In an era of molecular biology, continuing to stratify patients by anatomic-extent-of-disease-at-detection may be detrimental to individual patients. The TNM staging system does not "cleave nature at her joints"; the same biologically driven cancer may appear at any stage. Therefore, stratifying patients to a therapy that is based on the TNM staging system may prevent a patient from receiving a curative therapy.

From this day forward, we must treat patients on the basis of the biology of their cancer, not by the location of the cancer at detection.

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