

Editorial

Predictive or non-predictive, prognostic or non-prognostic: Dilemmas generated through small retrospective studies

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In this issue of the *Journal of Gastrointestinal Oncology*, Katkooi et al report on the impact of the pro-apoptotic protein Bax and its ratio to the anti-apoptotic protein Bcl2 (Bax/Bcl2) by immunohistochemistry grading on the outcome of patients with colorectal cancer treated with curative intent surgery or curative intent surgery followed by 5-FU-based chemotherapy (1). The chemotherapy group was selected from a patient population treated with curative intent surgery followed by at least 3 months of infusional 5-FU based chemotherapy or 6 months of bolus 5-FU-based chemotherapy between the years 1987-1993. The surgical control group was matched to the chemotherapy group by age, sex, stage, ethnicity, differentiation, and tumor location. The investigators demonstrate a better survival outcome in patients with increased Bax expression vs low Bax expression in the absence of chemotherapy (surgery only). A trend towards a worsened survival outcome is noted in patients with increased Bax expression vs low Bax expression in the presence of chemotherapy. Furthermore, a low Bax/Bcl2 ratio was associated with a better survival outcome in comparison to high Bax/Bcl2 ratio in the presence of 5-FU based chemotherapy. The authors conclude that patients with higher Bax expression may not benefit from adjuvant chemotherapy.

One has to recognize that there are several limitations to the Katkooi study. First, the study suffers from a small and heterogeneous population. Twenty-five percent of patients investigated in this study had stage IV disease. Therefore, data extrapolation from this

heterogeneous population to adjuvant treatment in stage II-III disease cannot be applied. If the intent of the study is to investigate the impact of Bax on the effectiveness of adjuvant chemotherapy, it would have been advisable to limit the study population to stages II-III disease. Second, it is impossible from the current study design to conduct a meaningful evaluation of the impact of Bax or Bax/Bcl2 or p53 on OS within the surgical and chemotherapy groups. Since patient characteristics among the various biomarker groups had not been matched for other known risk variables of relapse within the surgery and chemotherapy groups, it would be possible that the divergence in outcome was due to an imbalance in other patient characteristics rather than due to Bax or Bax/Bcl2. Third, the study assumes no differences between various arms of 5-FU-based therapy in the chemotherapy arm, a finding refuted by prior randomized studies.

Is Bax prognostic? In the surgical group that did not receive chemotherapy, patients with elevated Bax had an improved survival. This would suggest that Bax over-expression is a positive prognostic factor. This could only be hypothesized if the high and low-Bax patients in the surgery-only arm were matched by stage, grade, and other relevant risk factors. This was not the case.

Is Bax/bcl-2 predictive of 5-FU response? In the patient undergoing surgery followed by 5-FU, patients with low bax/bcl-2 has a superior outcome than patients with high Bax/Bcl2. This would suggest that high bax/bcl-2 is predictive of 5-FU resistance. This can only be hypothesized if the two groups were matched for other risks of recurrence or progression. This was not the case.

Stage heterogeneity, small sample size, and the heterogeneity of 5-FU-based therapy, significantly limit the results from this study. In addition, the results do not support findings from a larger series evaluating the impact of Bax and Bcl2 expression on 5-FU-treated colorectal cancer patients (2). In a study of 188 patients treated with 5-FU based chemotherapy, low Bax expression was

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associated with a worsened outcome and patients with high Bax expression and low Bcl2 had the best outcome (2).

How do we move forward? This study illustrates the limitations of analyzing subjectively graded variables in a heterogeneous colorectal cancer population. It is time to recognize the complex interactions between variable prognostic markers of progression and disease resistance. Such interactions can only be tested in large patient populations whose baseline characteristics and outcomes were collected in a prospective controlled manner. A quantitative multi-gene RT-PCR assay for the prediction of recurrence in stage II colon cancer was recently developed by Genome Science using the QUASAR study population (3). While this assay is somewhat successful in categorizing stage II colon cancer into 3 distinct categories of risk of relapse, it failed to predict for benefit or lack off with 5-FU therapy. Oncotype DX profiling is one step in the right direction, but more work is clearly needed.

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