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EDITORIAL

# Significance of Pathologic Response to Preoperative Therapy in Pancreatic Cancer: The Future Ain't What It Used To Be

**Peter J. Allen, MD**

Memorial Sloan-Kettering Cancer Center, New York, NY

Over the past 10 years, our ability to predict the future of an individual patient with cancer has moved beyond T, N, and M. Although American Joint Committee on Cancer (AJCC) stage continues to be the bedrock of determining prognosis, a number of other factors have been identified that can stratify recurrence and survival outcome for a given patient within each stage category. Radiographic response, pathologic response, and a variety of molecular markers have been identified as important predictors of outcome. Complete pathologic response (cPR) to preoperative therapy has been found to be an independent predictor of survival in breast and rectal cancer, and the incorporation of this response into the AJCC staging system has been recommended for breast cancer patients who receive neoadjuvant therapy. [1,2] In a study from Memorial Sloan-Kettering Cancer Center of 200 patients undergoing resection for rectal cancer after preoperative chemoradiation, cPR trumped pretreatment stage in predicting outcome. [1] Importantly, in this study all patients underwent pretreatment and preoperative endorectal ultrasound (ERUS), and the pretreatment ERUS stage groupings were similar between patients who experienced cPR and those who did not. cPR was observed in 30% of patients (56% of patients with uT3N1 experienced cPR), and the survival in the cPR group was 90% at 5 years, compared with 68% in those without response. So, as the famous New York soothsayer Yogi Bera once said, "the future ain't what it used to be."

The current article out of Fox Chase Cancer Center further strengthens pathologic response as a predictor of survival in patients with resected pancreatic adenocarcinoma. In this study, 107 patients who received preoperative chemoradiation before pancreatic resection between 1987 and 2009 underwent histopathologic assessment of treatment response. Pathologic response was assessed in blinded fashion, and reported as percent fibrosis. Subsets were developed, and patients grouped into those with 0–49% fibrosis, 50–94% fibrosis, and >95% fibrosis. Major pathologic response (>95%) was identified in 21 of the 107 patients (19%), and eight patients (7%) had cPR. Median survival within the group of patients who experienced major response was 66 months, dramatically longer than in those who did not experience a response (minor response: median survival 17 months). Nodal status, margin status, and additional preoperative chemotherapy were additional factors found to be associated with survival. Multivariate analysis, however, found major pathologic response to be the only factor predictive of survival.

This study is important for several reasons. First, these data help to define a small subgroup of patients with pancreatic cancer who have exceptional outcomes for this disease. Within the group of patients who had major response and underwent resection there were no deaths within 18 months of diagnosis and median survival of 66 months. Tissue from these patients should serve as a valuable resource for identifying molecular differences between those with cPR and those with no response. These differences may allow further insight into the mechanisms of pancreatic adenocarcinoma, and allow identification of potential therapeutic targets. Furthermore, these data support pathologic response as a factor that should be considered for stratification in any post-resection trial of systemic therapy, and a factor that should be evaluated in decision-making for post-resection systemic therapy.

The strengths of this study however raise several important questions, the limitations of these data are several, and the conclusions should be viewed in context. First, the overall effectiveness of preoperative chemoradiation in this disease process has been remarkably low. In this study



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P. J. Allen, MD
e-mail: allenp@mskcc.org

over a 22 year time period, only 19 patients resected at a high-volume cancer center were found to have had major pathologic response to preoperative therapy (<1 patient/year). Dr. Hoffman and Fox Chase Cancer Center have been leaders in the development of neoadjuvant strategies for borderline and locally unresectable pancreatic cancer, and therefore one must assume a much larger denominator if all patients who were treated during this time period with chemoradiation for borderline or locally unresectable pancreas cancer were included. To put this in perspective, it would be interesting to know how many patients were treated over the 22 year time period for borderline or locally unresectable pancreatic cancer who did not go on to resection. In addition, because the denominator only included resected patients, and because survival was calculated from date of diagnosis rather than date of resection, one might expect survival to be more favorable in those who underwent resection farther out from diagnosis. Could this be the reason why additional chemotherapy was found associated with improved survival on univariate analysis?

The data presented in this study suggest that pathologic response may improve our ability to predict and stratify outcome in patients resected following neoadjuvant therapy for pancreatic cancer. Predicting the future is a powerful ability; however, the greater power—and more daunting challenge—is the ability to change it. The downside of pathologic response in pancreatic cancer is that this response can only be obtained after many months of treatment, which for the majority of patients will be largely ineffective. Efforts at changing outcome based on pretreatment factors, or factors that can be assessed very shortly after initiation of treatment, are necessary. In other diseases these efforts include *BRCA* mutational status and poly ADP ribose polymerase (PARP) inhibition in breast cancer (now being applied to pancreatic cancer), microsatellite instability, and response to 5-fluorouracil (5-FU)-based chemotherapy in patients with colon cancer, and early positron emission tomography (PET) response as a method to guide treatment in esophageal and gastro-esophageal (GE) junction cancer. [3–5] Pathologic response may prove to be a powerful predictor of outcome in patients with pancreatic adenocarcinoma. Hopefully, this knowledge can be used to design methods for changing that outcome.

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