Can Prognosis Be Modified in Pancreatic Cancer?

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In this issue, Nakagawa and colleagues provide an evaluation of the Naples prognostic score (NPS) in patients with resected pancreatic cancer.¹ Their review, while retrospectively applied to a cohort of resected patients at their institution, provides a novel approach to evaluate short-term and long-term outcomes in patients with this aggressive disease, with a focus on simplicity of application. Importantly, they are able to demonstrate that the NPS is an independent predictor of survival.

While several scoring systems, including standardized pathologic reports, have served to help predict prognosis of patients undergoing oncologic therapy, many have failed to provide helpful information preoperatively, at a time when risk stratification arguably matters the most. As the authors eloquently highlight, factors such as tumor size, nodal metastases, lymphovascular invasion, perineural invasion, and grade of differentiation are all critical prognostic factors that are powerful discriminators of survival. However, these data are only available postoperatively and following complete tumor extirpation.

In their report, the authors are able to apply the simple NPS to patients preoperatively using previously described cutoffs for individual components including serum albumin, total cholesterol, neutrophil-to-lymphocyte (NLR) ratio, and lymphocyte-to-monocyte (LMR) ratio. These combined components and cutoffs have previously been evaluated following colorectal surgery where they provided adequate discriminatory capacity with important prognostic implications.² The authors' decision to apply NPS in resected pancreatic cancer is thus a commendable

endeavor, particularly with the outstanding results achieved in their study. By grouping patients into 3 categories based on preoperative laboratory values (groups 0, 1, and 2), the authors were able to demonstrate marked median overall survival differences across the groups. The best performing group, comprising 22 patients (11% of the cohort), had a remarkable median overall survival of 103 months. The NPS provided similar discriminatory potential for median recurrence-free survival across the groups, highlighting the powerful prognostic capacity of NPS preoperatively. Unfortunately, multiple comparison statistical testing was not conducted to determine where differences arose from but, importantly, patients appeared relatively well-matched according to both demographics and final pathologic review. Objective multivariable analysis confirmed the NPS as an independent prognostic factor, along with other expected factors on both multivariable and univariate analyses that confirmed the validity of the authors' findings and reliability of their cohort.

Having achieved an important feat in being able to provide prognostic information based on simple laboratory data preoperatively, we couldn't help but wonder whether these validated components, including albumin in particular, may be modifiable. At our institution, we are currently enrolling patients in a multimodal exercise and nutrition phase II prehabilitation clinical trial that aims to optimize pancreatic cancer patients prior to pancreatectomy.³ While the authors describe the role of albumin in the context of inflammation and proinflammatory cytokines that may reduce albumin concentration, the exact modalities by which exercise and nutritional optimization serve to increase albumin levels are complex and likely multifactorial, and may potentially include attenuation of proinflammatory states. Altering inflammation would feasibly also extend to the other NPS components, including NLR and LMR, which themselves depict overall inflammation. Similar to albumin, the role of serum cholesterol levels, which have been reported to correlate with

progression of cancer, open a door on the role of statins and other cholesterol-modifying agents, which have already been explored in oncology and with interesting positive repercussions in some instances.⁴ Thus, can prognosis be modified in pancreatic cancer?

It has long been stipulated that exercise and nutrition may play a role in oncologic survival. Aside from reducing complication rates and surgical frailty, the components examined by Nakagawa and colleagues provide additional mechanisms via alteration of inflammatory states by which multimodal prehabilitation regimens may enhance prognosis in patients with pancreatic, and other, cancers. Although these questions require further exploration and the mechanisms responsible have not yet been elucidated, what is clear is that engaging patients in their own care may provide a golden opportunity to improve their outcomes. This is particularly relevant as the care of pancreatic cancer continues to move in a neoadjuvant direction, and surgery becomes a goal that lies months ahead from diagnosis.

It remains to be seen whether applicability of the NPS is feasible in patients who receive neoadjuvant therapy. However, despite stark differences between Eastern and Western patient populations and surgical care, such as body mass index, aggressive approaches to arterial reconstruction without neoadjuvant therapy, and different adjuvant therapies, including S1, these data clearly highlight the importance of identifying novel predictors of survival preoperatively that are potentially modifiable. With only

37% of the author's patients receiving adjuvant therapy, the burden of pancreatectomy is clearly evident across this Eastern patient cohort as well, highlighting once again an important advantage of the total neoadjuvant therapy approach in patients with pancreatic cancer.⁵

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