

Editorial

From Bad to Worse: Prognostic Factors in Pancreatic Cancer

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The search for more accurate prognostic factors in oncology is nearly as old as the specialty itself. It is rudimentary that the ability to predict accurately the risk of recurrence confers numerous benefits including (1) suggesting the appropriate therapy for each patient (i.e., not overtreating or undertreating); (2) allowing precise stratification of patients for clinical trial enrollment and; (3) providing patients with information about their risk of disease recurrence and death so they can make informed choices regarding their treatment and handling of personal affairs. Although cancer staging systems are accurate in stratifying patients into four primary prognostic groups, they lag far behind our increasing understanding of the molecular heterogeneity within cancers of a particular tissue type and stage. Although we can now determine many of the changes in both gene and protein expression within a given tumor, determining which of those changes is most relevant to prognosis often remains elusive. It is clear, however, that for most tumor types, defining molecular changes that can identify those patients with stage I cancer who are at high risk for recurrence or, conversely, those with stage III cancer who do not require adjuvant chemotherapy would be a tremendously powerful tool.

In this issue of the *Annals of Surgical Oncology*, Yamamoto et al.¹ report their findings that increased expression of the valosin-containing protein (p97) is associated with lymph node metastasis and poorer prognosis for patients with resected pancreatic cancer. p97 is a recently described adenosine triphosphatase (ATPase) involved in the ubiquitin-dependent degradation of I κ B α , an inhibitor of NF κ B. It is hypothesized when p97 is overexpressed, NF κ B levels rise and cancer cell apo-

ptosis is inhibited. Using immunohistochemistry, the authors examined p97 expression in tumors from 83 patients with resected pancreatic cancer. Tumors were scored as low or high expressors, relative to the staining of adjacent non-neoplastic pancreas. The authors found that p97 expression, T and N stage, and histologic differentiation correlated with survival. High p97 expression was also correlated with the risk of lymph node metastasis. In patients whose tumors had low p97 expression, 5-year actuarial survival was 70% for those patients with stage I and stage II disease versus 28% for patients with high p97 expressing tumors. For patients with stage III disease, survival was 38% versus 9% for low versus high expression of p97. The relative risk of death for patients with high expression of valosin-containing protein was increased 2.4 times, the same relative risk conferred by the presence of lymph node metastases. Poorly differentiated histology conferred a 6.4 times risk of death. The current study suggests that p97 may be an accurate prognostic marker in resected pancreatic cancer, although no more so than the known prognostic factors of stage and histology. Adjuvant therapy was inconsistently applied to this group and so no real comment can be made about whether this would change the prognostic accuracy of p97.

Certainly the authors' findings are of interest as they suggest the p97 protein may be a mediator of aggressive behavior in pancreatic cancer. Correlative studies, however, are always limited in that they cannot tell us whether the factor under study, in this case p97, is a cause or a consequence of aggressiveness. The authors suggest that their data demonstrate p97 can be useful as a prognostic factor in pancreatic cancer. The value of a prognostic factor must be measured by the following tests: (1) Does the new marker provide additional information not readily provided by more standard prognostic factors such as stage or grade? (2) If not, can the data from this new prognostic factor be more readily acquired (i.e.,) through a serum sample or without the need for a pathologic specimen)? And, most importantly, (3) Does

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the prognostic factor allow for a new and rationale change in patient management that results in either in improved survival or quality of life outcomes? Before the Yamamoto et al. study, numerous other candidates have been put forth as possible prognostic factors in pancreatic cancer. These include expression of p53, cyclin D, and mutations in *K-ras*, among others.²⁻⁴ None of these factors, however, pass the tests outlined above. It is a sad fact that in 2004, pancreatic cancer remains a nearly uniformly fatal disease. Whereas patients with stage I disease at diagnosis clearly have a longer median survival than those with stage IV disease, this difference remains in the range of 12 to 18 months at best. For patients with resectable disease, true 5-year survivorship is in the range of 10%.⁵ As the authors point out, this is because many patients with "resectable" tumors harbor occult metastatic disease. For all practical purposes then, nearly every patient with pancreatic cancer has either visible or occult metastases at diagnosis. As such, no subgroup has a "good" prognosis. A little better, a little worse, perhaps, but good in the sense that any patients with resected pancreatic cancer should be withheld from consideration of adjuvant therapy studies, certainly not. Although interesting and it is hoped of importance in the future, the current utility of prognostic factors for patients with resectable pancreatic cancer is minimal. In the Yamamoto et al. study, low expression of p97 was associated with a 70% actuarial 5-year survival for patients with stage I and stage II disease. In fact, even the "bad" group of high expressors had a 28% actuarial survival. These are survival statistics that no large clinical studies of pancreatic cancer have ever even approached. It is, therefore, tempting to ascribe some of the authors' find-

ings to a relatively small sample size. This is not to say they are unimportant. Rather, the significance of their findings lies predominantly in their promise as possible clues to understanding the molecular basis for the aggressive clinical behavior of pancreatic cancer. The Yamamoto et al. study raises numerous important questions regarding the p97 protein. Does overexpression of p97 confer an aggressive phenotype on pancreatic cancer cells? If so, are these changes related to apoptotic resistance, increased invasiveness, angiogenesis, metastasis, or some other characteristic of the cancer cell? How is p97 expression regulated and does down-regulation of its expression reverse the malignant phenotype? The answers to these and other questions will ultimately define the importance of p97 in pancreatic carcinogenesis and whether determination of p97 expression will have a role in the clinical management of this deadly disease.

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