EDITORIAL – PANCREATIC TUMORS

Exosomes from Pancreatic Juice: A Step Closer to the Holy Grail?

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The readership of *Annals of Surgical Oncology* certainly needs no reminders about the inherently poor prognosis faced by pancreatic cancer patients. The past decade has witnessed an increasingly sophisticated understanding of the pancreatic ductal adenocarcinoma (PDAC) genetic and transcriptional landscape, an appreciation and characterization of the complexities of the tumor microenvironment and tumor metabolism, and the resultant identification of numerous novel therapeutic targets and new drugs. Despite this, the only improvements in patient outcomes have resulted from cytotoxic drug combinations.

Late diagnosis, relative to local and distant tumor progression, continues to forestall our ability to make a major impact in this disease. Thus, it has become increasingly clear that earlier diagnosis is the holy grail if we are to make disruptive change in the still single-digit 5-year survival facing our patients.

The efforts to conquer this disease have been buoyed by the work of numerous surgeon scientists who have developed animal models, identified critical components of its biology, defined the transcriptional landscape, and conducted practice-changing clinical trials.[1–5] In this edition of *Annals of Surgical Oncology*, Nakamura et al.[6] report a novel technique to isolate exosomes from pancreatic juice and the identification of exosomal microRNAs (miR)-21 and -155 as putative biomarkers for the diagnosis of PDAC. The authors studied 35 patients, 27 with PDAC and 8 with chronic pancreatitis, and found that the presence of either exosomal miR-21 or -155 resulted in an accurate diagnosis of pancreatic cancer 83% and 89% of the time, respectively. These numbers were improved when combining them with the results of pancreatic juice cytology. The authors openly cite several limitations of their study, including sample size and the fact that these samples required cannulation of the pancreatic duct, which puts patients at risk for postprocedure pancreatitis. Before considering limitations of the study further, it is important to speculate on how such a diagnostic might even fit into the landscape of an early detection initiative.

Pancreatic cancer remains a relatively low incidence disease compared with other malignancies that are the subject of screening, such as breast and colorectal cancer. Thus, screening mass populations remains wholly impractical as even tests with excellent performance characteristics would result in a greater number of false positive and false negative results than true positive tests. In addition, there remains the very practical consideration that even a perfect molecular diagnostic would be severely limited without a paired imaging study, as an accurate molecular diagnosis of early pancreatic cancer would leave surveillance imaging versus total pancreatectomy as the only rationale management options. Truly, the ideal scenario for pancreatic cancer diagnostics would be to identify incipient cancers that could be treated with prevention or so-called 'interception' strategies.[7]

Given these considerations, we can consider the Nakamura study as an intriguing start as they have identified a method to isolate exosomes from pancreatic juice, and have further demonstrated the stability of RNAs, allowing for molecular diagnostic testing. The study examined 27 PDAC patients, of whom 22 had lymph node metastases or inoperable disease; thus, this was a group of patients with advanced disease. They found that miRs were detectable in one patient with carcinoma in situ—an encouraging result, but larger confirmatory studies composed of patients with earlier cancers are needed. Ultimately, molecular diagnostics such as these must be studied prospectively in the context of screening programs for high-risk groups such as those harboring germline pathogenic variants that confer

cancer susceptibility. Many additional important questions are also raised by the authors' findings: (1) Might an enlarged panel of miRs provide even better performance characteristics: (2) Would it be feasible to improve the exosomal miR diagnostic by combination with more rudimentary assays such as next-generation sequencing for detection of common pathogenic alterations in genes such as Kras and p53? (3) How early in the disease course can we detect these alterations in miR expression? Although there are undoubtedly technical challenges, it is possible genetically engineered models could be employed to initially address some of these questions. Finally, it will be important to study exosomal miR levels in the context of patients without chronic pancreatitis as this will likely be more representative of a screening cohort. In fact, one might optimistically speculate that in light of such a comparator, the performance characteristics of the test might be improved.

In conclusion, the study by Nakamura et al. makes several important contributions to the field, most notably the technical advance in isolation of exosomes from pancreatic juice and the demonstration of proof of principle that this biologic resource can be probed as a diagnostic. One can only hope that this early experience can be validated by others, and, most importantly, serve as a building block toward the early diagnosis and ultimately the prevention of pancreatic cancer.

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