GUEST EDITORIAL

Pancreatic Ductal Adenocarcinoma

Recent Updates

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I began to work on carcinoma of the pancreas as a research area and to attend meetings that focused on the disease in 1972. Major topics of those early meetings included the overall low survival of patients with pancreatic ductal adenocarcinoma (PDAC), the infrequency of early diagnosis when the carcinoma was operable, the need for chemotherapy regimens that were more effective than 5-fluorouracil (5-FU) in advanced patients, epidemiology with emphasis on ways to reduce the incidence of the disease, the need for a tumor marker that was more effective than CA19-9 in finding small operable carcinomas, and the need for animal models.

Progress has been made in several of these areas. For example, the five-year survival of patients with PDAC is now reported as 8%¹ whereas earlier five-year survivals were often in the range of 5% but as low as 3% in some early series.² Some of this improvement can be attributed to a drop in operative mortality for pancreatic resection as specialized centers for treatment of PDAC have developed and fewer pancreatectomies are done in centers with a low volume (UpToDate, <https://www.uptodate.com/contents/overview-of-surgery-in-the-treatment-of-exocrine-pancreatic-cancer-and-prognosis>, last accessed July 2, 2018; registration required).

However, it should be noted that Gudjonsson,³ often a skeptic, using data as recent as 2013 estimates that the overall actual survival rate is hardly more than 0.3% for patients with PDAC. Pancreatectomy is regarded as the only potentially curative treatment, but only 15% to 20% of PDAC patients are diagnosed when they are operable (<https://www.uptodate.com/contents/overview-of-surgery-in-the-treatment-of-exocrine-pancreatic-cancer-and-prognosis>, last accessed July 2, 2018; registration required) and recurrence is frequent following resection.

Gemcitabine was approved for clinical use in the US in 1995. It is less toxic than 5-FU but disappointing in regard to improving long-term survival of patients with PDAC. More recently, combination therapies such as gemcitabine plus capecitabine or the Folfirinox regimen are proposed for advanced disease.

Luberice has evaluated the efficacy of modern treatments including earlier diagnosis, pancreatectomy, and improved adjunct therapy on long term survival in recent decades. He found that improvements were in short and intermediate term outcomes but not 5-year and longer survivals.²

Progress in imaging now allows detection of small neoplasms but the methods are not practical for mass screening due to the expense of computerized tomography (CT), MRI scans, and endoscopic ultrasound (EUS). No immunologically-detected tumor marker is established as better for early detection than CA19-9, a marker that is now used primarily to monitor the response to therapy and to detect recurrences in advanced patients.⁴

Chemically-induced rodent models and transgenic mouse models have been developed. The more recent of these use transgenic mice with genetic abnormalities that are based on genetic abnormalities found in human PDAC, especially KRAS mutations.⁵

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In general, research goals remain much the same today as those listed above. The following seven papers that comprise this special issue of *The American Journal of Pathology* address several of these goals.^{6–12} They reflect the changes in experimental approaches resulting from advances in molecular biology beginning with detection of genetic changes and molecular abnormalities in PDAC as mentioned in most of these papers including Ren, Liu, and Suriawinata.⁶ These authors discuss the pathology including characteristic genetic abnormalities of PDAC, by far the most frequent cancer of the human pancreas, with emphasis on its precursor lesions [high grade pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN)] that represent an incipient (*in situ*) stage of PDAC. The increasing use of endoscopic ultrasound to obtain fluid and cells for molecular and cytologic analysis is noted. Significant progress has been made in these areas during recent decades including the recognition that some PDAC arise from IPMN and MCN—cystic lesions that are detectable by imaging.

Identification of genomic abnormalities that are found in familial PDAC patients allows identification of individuals at high risk for developing PDAC who therefore qualify for close surveillance and screening to detect early pancreatic carcinomas, as discussed by Choda et al⁷ and also discussed in this issue by Diaz and Lucas.⁸ These authors also consider modifiable risk factors that may interact with inherited genetic factors predisposing to PDAC. In this context, the authors provide a brief mechanistic review of the epidemiology of PDAC. They also mention screening to detect multifocal high grade PanIN and high grade IPMN in addition to early invasive or resectable PDAC.

Lafaro and Melstrom⁹ analyze and discuss the mechanisms of protumor and antitumor effects of the characteristic desmoplastic stroma of PDAC. They point out that the stroma may comprise as much as 85% of the neoplasm. They epitomize their focus as follows: “This desmoplastic microenvironment may compromise tumor blood perfusion and oxygen delivery, in turn creating an obstacle for drug delivery.”^{9,pp.44} The authors then tick through the cellular and humoral elements of the stroma identifying several specific potential targets for therapy.

The review by Tesfaye, Azmi, and Philip¹⁰ examines the usefulness of microRNA (miRNA) in the diagnosis, treatment, and determination of prognosis of PDAC. miRNA-based approaches show promise as biomarkers for early diagnosis, as a new approach for therapy, and as biomarkers to follow the response of PDAC patients to treatment. Multiple studies are cited that support all three applications, but these studies have not yet yielded an application that is practical at the clinical level.

Gall et al¹¹ review progress in the use of circulating tumor cells (CTC) as a potential indicator of prognosis and response to treatment in PDAC. This group has previously

commented that isolation and study of circulating tumor cells (CTCs) is an expensive diagnostic test that requires careful evaluation before it is applied clinically in diagnosis and staging.¹³ Their interest extends to the role of cell-free DNA (cfDNA) in the diagnosis and treatment of PDAC. They suggest that evaluation of CTC has greater potential as a way to predict prognosis and monitor the results of treatment than as an approach for early diagnosis. However, cfDNA may contribute in both realms and has potential for application in early diagnosis. They maintain hope that CTCs and cfDNA may serve “as markers of diagnosis, prognosis, and response to oncological treatments.”^{11,pp.79}

It is bad news when a patient is found to have a pancreatic mass leading to a clinical (usually image-based) diagnosis of probable PDAC. Many patients with such a history have undergone pancreatectomy. The good news for some of these patients is the pathologic finding that the resected mass is not PDAC. Sometimes these patients are found to have autoimmune pancreatitis or less often other fibroinflammatory lesions such as follicular or groove pancreatitis as discussed succinctly by Zen and Deshpande.¹² Alternately the patient may be found to have a neoplasm other than PDAC that is characteristically benign or distinctly less malignant than PDAC (<https://www.uptodate.com/contents/pathology-of-exocrine-pancreatic-neoplasms>, last accessed July 11, 2018).

A major goal of several investigators who have contributed to this published symposium is to find molecular markers that can predict the presence of early stage invasive PDAC and allow localization with modern imaging methods so that the lesions can be resected. A second goal is to define molecular abnormalities in resected PDACs that can guide the selection of effective adjuvant treatment or systemic therapy of patients with advanced disease. These are worthy goals that may be achievable with current technologies.

As noted above, Luberice et al² have reviewed the impact of improvements in diagnosis and treatment of PDAC patients on their survival. They open their discussion by stating “Despite all the money, all the attention, all the tears, all the effort expended to combat pancreatic cancer over the past two decades, long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma has not increased.”^{2,pp.343–344} Despite recent progress, PDAC remains a highly invasive and almost uniformly lethal neoplasm that is difficult to diagnose when it is operable and often recurs following resection. Diagnosis at the *in situ* stage is even more difficult.

Perhaps a change in paradigm with greater emphasis on prevention is needed. For example, research goals could be focused on the finding of molecular markers that reliably suggest the presence of incipient (*in situ* stage) neoplasms even if the lesion is too small to allow its localization by imaging (as is likely for high grade PanIN). A blood-born marker would be ideal, but pancreatic juice aspirated from the duodenum might provide an alternate source. Then patients with such biomarkers could be treated with a

yet-to-be-identified systemic therapy that kills the malignant cells. An agent that is secreted in pancreatic juice would be ideal. Then the therapy would be analogous to the topical treatment of actinic keratoses using 5-FU to prevent skin cancers. These goals will require discovery and documentation of both markers for diagnosis of *in situ* stage neoplasms, especially high grade PanIN, and the response of these *in situ* neoplasms to treatment. Perhaps the use of transgenic mouse or *in vitro* organoid culture models can facilitate some of this documentation.⁵

Our current situation reminds me of the poem by Robert Frost, “Stopping by Woods on a Snowy Evening” (<https://www.poetryfoundation.org/poems/42891/stopping-by-woods-on-a-snowy-evening>, last accessed July 11, 2018). We are still in the woods and there are miles to go before investigators in these areas can “sleep.”

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