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Mini-review

Toward stratification of patients with pancreatic cancer: Past lessons from traditional approaches and future applications with physical biomarkers

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) has a high mortality rate and outcomes have not improved substantially for decades. Significant attention has focused on the biological drivers of the disease, and preclinical work has pointed to multiple biomarker candidates and therapeutic avenues. However, translation of these promising biomarkers and treatment strategies to patients has not been overwhelmingly successful. New strategies to account for the significant heterogeneity of the disease are needed so that rational treatments can be administered. Here, we focus on how physical sciences-based approaches may play a role in stratifying patients for clinical trials, and how this view of PDAC may reinvigorate treatment strategies that have been abandoned after "failing" to fulfill their potential in unselected patient populations. By complementing biological approaches, the development of physical biomarkers of PDAC may help deliver on the promise of personalized medicine for this devastating disease.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal tumor with a 5-year survival of less than 7.2% with about 48,960 new cases in 2015 [1]. Chemotherapy is the mainstay of treatment for non-surgical candidates, who represent about 80% of all patients. However, results have been unsatisfactory, with few chemotherapy agents and limited targeted drugs showing any durable efficacy. Unfortunately, for the 10–20% of patients with resectable disease, the results are also poor, indicating that new approaches are needed for all stages of PDAC.

The common clinical practice regarding newly diagnosed resectable and borderline resectable PDAC continues to be adjuvant chemotherapy following surgical resection. The general principle with this approach is to provide systemic control over a disease that is potentially widespread in all patients at any given stage. Alternatively, Evans and associates pioneered the idea that systemic therapy prior to resection could help select the patients with early stage tumors who would benefit from surgery [2].

The goals of neoadjuvant therapy are to increase the probability of successful surgery and to reduce the risk of local and distant recurrence. Preoperative therapy allows for the delivery of chemotherapy and/or ionizing radiation to an intact primary tumor; furthermore, it allows the patients to regain physical strength and improve their performance status, which may be compromised after surgery [3]. Neoadjuvant therapy has been extensively studied during the past two decades, showing that the approach is safe and well tolerated [4]. In addition to selecting out patients who have aggressive biology and who would not have benefited from a radical surgery, the preoperative therapy provides some prognostic information for those who do undergo resection, as the extent of pathological response to therapy has been associated with outcomes [5]. However, only a small minority of patients achieves an excellent response to neoadjuvant therapy (less than 10% viable tumor cells), and methods to identify these patients *a priori* are currently lacking in the clinic. Namely, with the exception of CA19-9, a biomarker with several limitations, there are no viable prognostic or predictive biomarkers for PDAC [6].

Our group has attempted to address the lack of useful biomarkers for PDAC by focusing on the physical properties of PDAC [7]. This approach may also help in the design of rational therapeutic strategies to improve responses for the majority of patients who have resistant disease. Moreover, recent studies suggest that this approach will have application to emerging therapeutic strategies. In this article, we will review this literature and explain how physical sciences-based approaches may improve our understanding of PDAC and the clinical management of this disease.

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Clinical relevance of mass transport properties in PDAC

It is well accepted that PDAC has significantly different physical properties than the surrounding pancreas parenchyma and that there is significant heterogeneity in these properties from patient to patient (Fig. 1). In fact, radiologists utilize this physical differential to identify tumors in the pancreas. During contrast-enhanced scans, PDAC is characteristically hypodense relative to the normal pancreas. This imaging feature of the disease is directly related to the underlying pathological physical features in the tumor microenvironment (TME) and the cancer cells. This is a classic example of a concept called transport oncophysics [7].

Transport oncophysics describes how the physical aberrations of cancer exist on multiple scales, including the molecular, cellular, extracellular, vascular, and whole organism levels [8] (Fig. 2). PDAC is a prime example of this concept, as it demonstrates differential expression of cellular transporters, extensive but variable amounts of desmoplasia, a low vascularity with many dysfunctional blood vessels, and metabolic derangements that may contribute to the wasting syndrome that many patients exhibit at advanced stages. The oncophysics view of the disease process has application to tumor progression, metastasis, and treatment. In fact, several important translational and clinical studies support the multi-scale view of cancer [9].

Conceptually, the transport of drug molecules like gemcitabine to PDAC cells involves movement across the deranged and non-functional tumor vasculature, the dense stromal compartment, and the cellular transporters of nucleosides, such as human equilibrative nucleoside transporter (hENT1) [10]. Each of these factors contributes to the multi-scale mass transport dysregulation that may account for the significant heterogeneity in the inter-patient and intra-tumoral delivery of gemcitabine [7]. To investigate the influence of mass transport characteristics of PDAC tumors on the delivery and the cellular DNA incorporation of gemcitabine, our group conducted a clinical trial in which gemcitabine was intraoperatively infused in 12 previously untreated patients during curative-intent resection of PDAC. Interestingly, drug incorporation into tumor cells was correlated with quantitative volumetric measurements of tumor enhancement taken from pre-surgery pancreatic protocol CT images. Moreover, as a demonstration of the principle of transport oncophysics (i.e., multi-scale physical aberrations), we observed that the highly variable delivery of gemcitabine to the cancer cells was dependent on both the amount of stroma in the PDAC tumor and the expression level of hENT1 [11]. This study has provided new insight to drug delivery in PDAC and opens the avenue to use quantitative imaging to characterize the disease [7]. The observed dependency of gemcitabine DNA incorporation on microenvironment (i.e., stroma) and cellular factors (i.e., hENT1 expression) in this study may explain the failure of some clinical trials that did not take into account such multi-scale transport dysregulation. For instance, a gemcitabine drug-lipid conjugate did not show a survival difference in patients with low hENT-1 expression compared to gemcitabine alone [11], possibly because of the lack of stratification according to other transport characteristics, especially the variable stromal content of the tumors.

The characterization of the physical properties of PDAC may lead to more effective personalized PDAC treatment. This approach has application to numerous therapeutic strategies for PDAC,

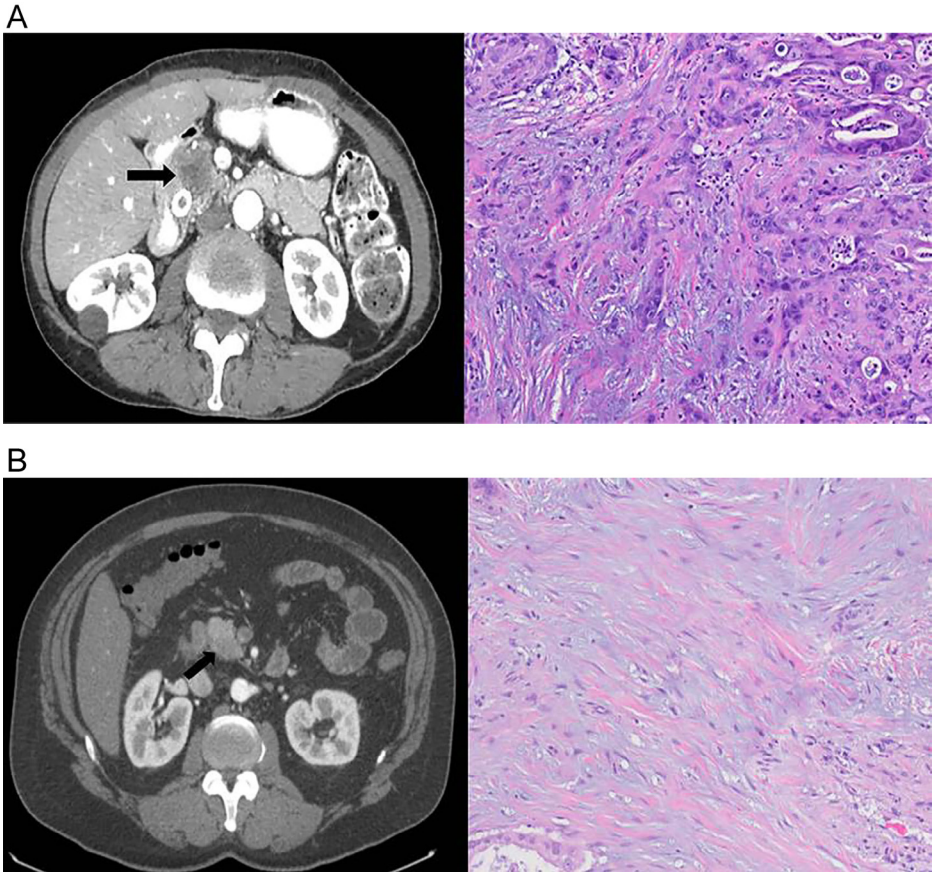

Fig. 1. Imaging and pathological features of pancreatic cancer. (A) A hypodense tumor in the head and neck of the pancreas (arrow) with low amounts of stroma relative to the cancer cells. (B) A relatively isodense tumor in the uncinated process of the pancreas (arrow) with high amounts of stroma (pink) relative to the cancer cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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