Opinion

Lets add a "S" to PDAC: the subtypes of pancreatic ductal adenocarcinoma S

Abstract

The incidence of pancreatic cancer, the 4th leading cause of cancer death in the US is increasing worldwide. Above 80% of these cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection remains the only curative treatment, the key lies in early screening, proper classification and right therapy. With advancing researchers have better tools to understand Pancreatic Duct Adenocarcinoma or PDAC. This brings the hope of better screening and diagnosis, accurate subtyping of pancreatic cancer and fine tuning the treatment to the right stage and tumor biology. In this data driven era it would be prudent for academician and clinicians to sub categorize PDAC into its various types and treat them as different entities and not club them together for therapy or trials. For Academician it would help achieving statistical significance in studies and for clinicians we would be not be giving a placebo drug to a vast number of patients.

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Introduction

The incidence of pancreatic cancer, the 4th leading cause of cancer death in the US is increasing worldwide. Even though the cure rate has increased in 30 years, it is very low approximating at less than 7%. It, is often diagnosed at a very late stage, when curative treatments are not very good. Above 80% of these cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection remains the only curative treatment, the key lies in early screening, proper classification and right therapy. With advancing technologies and ease of availability of them, researchers have better tools to understand Pancreatic Duct Adenocarcinoma or PDAC. This brings the hope of better screening and diagnosis, accurate subtyping of pancreatic cancer and fine tuning the treatment to the right stage and tumor biology.

PDAC is the most common form of pancreatic cancer. The causes and risk factors of PDAC are largely unknown. Various treatment modalities have been tried for management of PDAC. The methods have usually evolved as a result of anecdotal experiences and clinical trials. Very few randomized trials have shown to drastically alter the way the PDAC are managed. Most of the trials suffer from inadequate statistical significance. This has been hypothesized to PDAC not being one disease but an aggregate of many. The scientific community does think the fundamental differentiation in PDAC lies in its genetic mutations and variable activation of them. The inherited genetic mutations and associated syndromes are rare. Sporadic mutations are much more common. For example p16 and TP53 genes mutations are found in both inherited and sporadic diseases, while KRAS, BRAF, and SMAD4 mutations are usually found in sporadic disease. These genetic mutation signatures give each PDAC a different prognosis and maybe a different management. Proteomics helps identify the activity of the gene mutations. They give more functional accuracy in the data whereas the genomics give more of the physical information. The proteomics technology has improved a lot. With easy of testing, its cost and accuracy has helped fuel pancreatic cancer research. The large amount of Genetic Study on PDAC has failed to effect clinical decision making. It is becoming evident that genetic changes alone are insufficient to understand this disease and we need to add proteomic data to better understand it. Similarly phosphorylation of protein adds more data to the already available proteomic and genetic data. It lets us know which proteins are active.

The challenge has been to Subtype the PDAC and desegregate all these PDAC so that we do not bunch up different diseases in the same pool hoping one treatment will treat all of them. This would help us in getting a better statistical significance in future clinical trials. With newer techniques the community has been able to subtype PDAC differently. None of the classification system has been universally accepted thus this field is thus in a stage of exponential growth and promise. The first classification was attempted in 2011. It has been challenged and updated with newer classification coming out more recently in 2015 and 2016.

Collisson in 2011 used Gene expression analysis to subtype it into "classical", "quasi-mesenchymal (QM)", and "exocrine-like". They had used 62 designated gene signatures.

The classical subtype had high expression of adhesion-associated and epithelial genes.

The QM (quasi-mesenchymal) subtype showed high expression of mesenchyme associated genes.

The exocrine-like subtype showed relatively high expression of tumor cell derived digestive enzyme genes.[1]
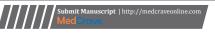
Moffitt on genetic analysis subtyped it into two tumor subtypes on the basis of two different tissues. "classical" and "basal-like" on the genetic analysis of the ductal cells and "normal" and "activated" on the basis of the stromal cells.

The Classical subtype fared better clinically than the "basal- like". The team also studied the stromal cells of PDAC and subtyped the tumor in to "normal" and "activated" stromal subtypes. Patients with activated stromal subtype had a worse prognosis.[2]

Bailey identified 32 genes that are consistently mutated in pancreatic tumors. On analysis of gene activity it revealed four distinct subtypes of PDAC "Squamous; "Pancreatic progenitor "immunogenic" and "aberrantly differentiated endocrine exocrine (ADEX)".

Squamous tumors had p53 mutations among others and were found to have a poor prognosis.

Pancreatic progenitor tumors had aberrant expression of genes involved in early pancreatic development.

ADEX tumors had aberrant activity of genes involved in KRAS activation, exocrine, and endocrine differentiation.

Immunogenic tumors had aberrant activity in genes regulating immune pathways.[3]

Conclusion

In this data driven era it would not be scientifically prudent for academician and clinicians to put all kinds of PDAC in the same limb of a clinical trial. For Academician it would only surmount to bias and achieving statistical significance very difficult, while for clinicians we would be knowingly giving a placebo drug to a vast number of patients. Therefore it's wise to follow and grow the growing field of Subtyping the Pancreatic Ductal Adenocarcinoma.

References

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