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Review article

Morphological heterogeneity in ductal adenocarcinoma of the pancreas – Does it matter?☆

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ABSTRACT

Morphological heterogeneity is a common finding in pancreatic ductal adenocarcinoma. Inter- and intra-tumour heterogeneity relates not only to the microscopic appearances of the tumour cell population, but pertains also to other essential aspects of the cancer, including the grade of differentiation, growth pattern and desmoplastic stroma. While the existence of considerable morphological variation is well known among pathologists, it is usually not fully appreciated by the wider community. Morphological heterogeneity in pancreatic cancer is only partially represented in the WHO classification, and current pathology guidelines do not recommend reporting on morphological variation other than the conventional variants of ductal adenocarcinoma. Although tumour heterogeneity is increasingly recognized as a major determinant of therapeutic response, morphological heterogeneity has been left unconsidered as a possible proxy for underlying aberrations – genomic or otherwise – that determine the effect of treatment. Various aspects of morphological heterogeneity in pancreatic ductal adenocarcinoma are illustrated in this article and discussed along with the possible implications for patient management and research.

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Introduction

Pathology is generally regarded as the backbone of diagnostics in patients with pancreatic ductal adenocarcinoma (PDAC). According to current best practice, a pathology report should confirm the diagnosis of PDAC and exclude other disease, provide the pT- and pN-stage and additional descriptors such as margin status and, if applicable, evaluate tumour regression after neoadjuvant

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treatment. National and international pathology guidelines do not encourage pathologists to record any morphological features of a pancreatic cancer beyond the mere statement of the tumour entity, i.e. ductal adenocarcinoma or one of its variants according to the WHO classification [1–7]. While standardized and proforma pathology reporting of PDAC has undoubtedly contributed to improved diagnostics, it has also resulted in a loss of appreciation of the morphological variation that exists between and within individual tumours that are recorded under the diagnosis PDAC. As a consequence, the histological picture of pancreatic cancer is at risk of becoming cartoon-like in its simplicity, holding for no more than an adenocarcinoma with exuberant desmoplastic stroma. The prominent *morphological* diversity of the cancer is largely ignored, while attention focusses on *molecular* heterogeneity and complexity. Morphological heterogeneity in PDAC has attracted little research interest, despite its potential use as a routinely assessable criterion of an integrated histological-molecular classification of PDAC.

This article does not result from systematic analysis but rather provides a brief overview of the wide morphological heterogeneity that is commonly observed during routine H&E examination of PDAC. Morphological variation of both the cancer cell population and tumour stroma will be illustrated, and possible implications for diagnostics and research will be discussed.

Intertumour heterogeneity

Morphological variation of PDAC is to some extent reflected in the WHO classification by the inclusion of so-called variants and *patterns* of ductal adenocarcinoma [7,8]. The latter encompass PDACs that differ in histological appearance, i.e. a clear cell, foamy gland or large duct pattern (Fig. 1), but are not associated with differences in biology, genetics or prognosis [7,9–12].

Variants of PDAC do not only exhibit a distinct morphological appearance, but differ also prognostically and may have a different molecular signature [8,13,14]. Variants of PDAC include adenosquamous, colloid, signet ring cell, medullary, hepatoid and undifferentiated carcinoma with or without osteoclast-like giant cells. Most of these variants have also been described in other parts of the digestive system and may share underlying molecular and pathogenetic factors. Medullary carcinoma, for instance, represents a rare variant of both pancreatic and colonic cancer, which is

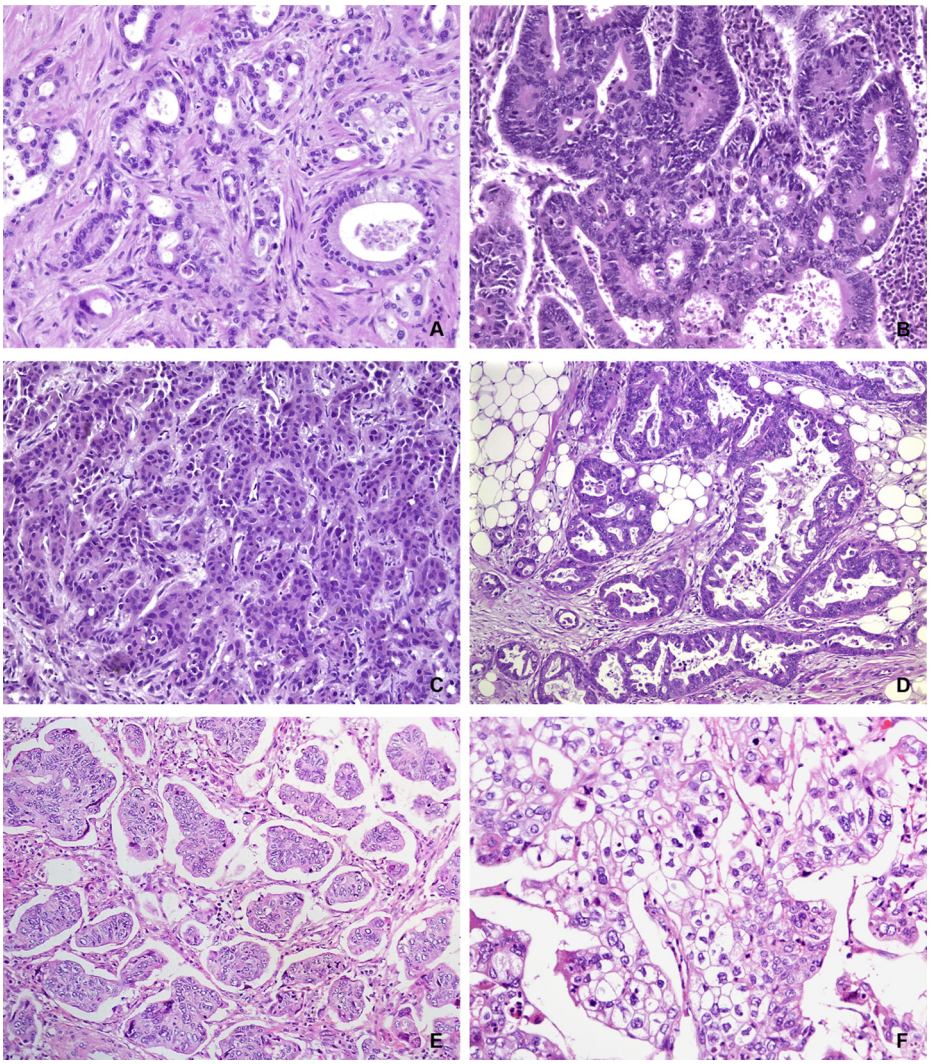

Fig. 1. Morphological heterogeneity in pancreatic ductal adenocarcinoma. Morphological appearances in figures A–C are described in the WHO classification as pancreatobiliary type (**A**), intestinal type (**B**) and clear cell pattern (**F**). Divergent histological appearances of PDAC in **C**, **D** and **E** have not been formally described. Figures A–D stem from the same tumour, i.e. represent intratumour heterogeneity.

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