

Solid Tumour Section

Review

Pancreatic tumors: an overview

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Abstract

Review on pancreatic tumors with data on clinics, and the genes implicated.

Classification

Note

The classification system here is adapted from those outlined in both the AFIP Atlas of Tumor Pathology Fourth Series (2007) and WHO Classification of Tumors of the Digestive System (2010). Pancreatic tumors can be subdivided on various criteria, such as their gross features (i.e., solid vs. cystic), anatomic location (i.e., intraductal), histogenesis (i.e., epithelial vs. non-epithelial) or clinical behavior.

Classification

Epithelial tumors

Cystic

Serous neoplasms

- Serous cystadenoma
- Microcystic serous cystadenoma
- Macrocystic serous cystadenoma
- Solid serous cystadenoma
- Von Hippel-Landau (VHL)-associated serous cystic neoplasm
- Serous cystadenocarcinoma

Mucinous cystic neoplasm (MCN)

- MCN with low or intermediate grade dysplasia
- MCN with high grade dysplasia
- MCN with associated invasive carcinoma

Intraductal papillary mucinous neoplasms (IPMN)

- IPMN with low or intermediate grade dysplasia
- IPMN with high grade dysplasia
- IPMN with associated invasive carcinoma

Intraductal oncocytic papillary neoplasms (IOPN)

Intraductal tubular neoplasms

Cystic acinar neoplasms

- Acinar cell cystadenoma
- Acinar cell cystadenocarcinoma

Solid

Invasive pancreatic ductal adenocarcinoma (and its variants)

- Tubular adenocarcinoma
- Adenosquamous carcinoma
- Colloid carcinoma
- Medullary carcinoma
- Hepatoid carcinoma
- Signet ring cell carcinoma
- Undifferentiated carcinoma
- Undifferentiated carcinoma with osteoclast-like giant cells

Acinar cell carcinoma

Neuroendocrine neoplasms

- Neuroendocrine microadenoma
- Neuroendocrine tumors (NET)
 - NET G1
 - NET G2
 - Neuroendocrine carcinoma (NEC)
 - Small cell NEC
 - Large cell NEC
 - Functional NETs (associated with clinical syndrome)
 - Insulinoma
 - Gastrinoma
 - Glucagonoma
 - Serotonin-producing NET
 - Somatostatinoma
 - VIPoma

Mixed tumors (combined acinar, ductal and/or endocrine differentiation)

Solid-pseudopapillary neoplasms (SPN)

Pancreatoblastoma

Non-epithelial tumors (rare)

Mesenchymal tumors (various histologies, benign or malignant)

Lymphangioma

Lymphoma

Mature cystic teratoma

Secondary tumors (including metastasis)

Non-neoplastic tumors and other lesions presenting as masses (partial list)

Cystic

- Groove pancreatitis (paraampullary duodenal wall cyst)

- Pancreatic pseudocyst

- Ductal retention cyst

- Congenital cyst

- Foregut cyst

- Lymphoepithelial cyst

Solid

- Chronic pancreatitis

- Lymphocytic sclerosing pancreatitis (autoimmune pancreatitis)

- Heterotopic spleen

Clinics and pathology**Note**

The vast majority of malignant pancreatic tumors (>85%) are pancreatic ductal adenocarcinomas (PDAC), the focus of this section.

Etiology

An evolving consensus arising from lineage tracing studies in animal models implicate acinar cells (and not ductal epithelium) as the likely cell of origin for PDAC. Precursor pancreatic intraepithelial neoplasia (PanIN) lesions have been shown to arise in the context of inflammation and acinar cell injury through a transitional process referred to as acinar-to-ductal metaplasia (ADM). ADM and PanIN formation is facilitated by oncogenic KRAS2 in combination with other molecular events and contributing factors (Morris et al., 2010). The concept of chronic inflammation and injury to the pancreas as an inciting event and/or promoter of pancreatic cancer progression is bolstered by the significantly increased (50-80 fold) risk of PDAC seen in patients with hereditary pancreatitis, as well as an increased risk for PDAC associated with the occurrence of chronic pancreatitis in the general population.

Epidemiology

The vast majority of PDAC arises sporadically. Age is a significant factor linked to the development of pancreatic cancer, with more than 80% of cases occurring after 60 years of age and only rare cases before the age of 40. Various dietary, lifestyle and environmental factors have been correlated with an increased risk for PDAC. A partial list of risk factors includes cigarette smoking, diets high in fat and total

calories, obesity, prior gastrectomy and certain occupational (i.e., coal gas and metal workers) and chemical exposures (i.e., benzidine, solvents, DDT and gasoline). Diets high in fruits and vegetables, folate and vitamin C are reported to be protective. Chronic pancreatitis and longstanding diabetes mellitus are also linked to an increased risk of pancreatic cancer (Yadav and Lowenfels, 2013). The development of chronic pancreatitis or adult-onset diabetes mellitus has been shown to be temporally linked to an increased risk for the subsequent development of PDAC, although it is unclear to what extent these events represent preceding causal factors as opposed to early manifestations of clinically undetected or nascent PDAC.

Approximately 10% of PDAC have familial inheritance, although only a minority (~20%) of familial PDAC has been linked to a known genetic syndrome or causal gene mutation. Hereditary syndromes associated with familial pancreatic cancer (along with their cumulative lifetime risk for developing PDAC by age 70) include: FAP (5%), hereditary breast and ovarian cancer associated with BRCA1/BRCA2 (5%), Lynch syndrome (<5%), FAMMM (17%), Peutz-Jeghers (36%), as well as cystic fibrosis (<5%) and hereditary pancreatitis (40%) linked to PRSS1 and SPINK1. (Templeton and Brentall, 2013).

Clinics

Clinical presentation is often non-specific for PDAC, which along with a lack of a viable early screening strategy for the general population, contributes to the late detection of disease in many patients. Some common presenting symptoms include epigastric pain radiating to the back, weight loss, jaundice and/or light colored stools (more typically for tumors in the head of the pancreas), digestive problems, anorexia, nausea, pancreatitis-related symptoms, new-onset diabetes and even depression. Diagnostic imaging techniques include computerized tomography (with PDAC commonly presenting as hypodense mass with possible pancreatic and/or bile duct dilation), endoscopic ultrasound or endoscopic retrograde cholangiopancreatography (ERCP).

Pathology

Precursor lesions that can give rise to invasive PDAC include pancreatic intraepithelial neoplasia (PanIN), IPMN and MCN. A majority of invasive PDAC arises from PanIN, dysplastic ductal proliferations showing variable epithelial atypia. PanINs are typically not recognized grossly and are generally smaller than 0.5 cm. Most IPMNs tend to be greater than 1.0 cm in size. A consensus classification system for PanIN lesions based on increasing cytologic atypia has been adopted (PanIN1A, 1B, 2 or 3). There is a parallel stepwise accumulation of molecular events found in PDAC associated with increasing PanIN grade (Hruban et al., 2001). IPMN are cystic or solid mass forming lesions

arising within the ductal tree itself, typically associated with abundant mucin production and demonstrating a papillary growth pattern of columnar epithelium of gastric foveolar, intestinal and/or pancreaticobiliary differentiation. IPMNs involving the main pancreatic duct (main-duct type) versus those isolated to side-branch ducts (branch-duct type) are distinguished clinically because of a higher risk of malignant progression associated with the former. Unlike IPMN, MCNs are mucinous cyst-forming lesions that do not communicate with the ductal system. MCNs almost exclusively occur in women (>95%) and arise at a median age of 40-50 years. The histologic sine qua non for MCNs is their distinctive ovarian-type stroma (Basturk et al., 2009).

Most PDAC are solid tumors and arise in the head of the pancreas (~70%), with the remainder occurring in either the body and/or the tail of the pancreas. Many PDACs invade beyond the pancreas itself to involve peripancreatic soft tissues with variable direct extension into adjacent anatomic structures, which depending on the location of the primary tumor may include the bile duct, ampulla, small or large bowel, peritoneum, stomach and spleen (pT3). Involvement of the celiac axis or mesenteric artery constitutes locally advanced disease (pT4). Common sites of distant metastatic spread include the liver and lungs, although nearly every other organ site has been shown to be involved at lesser frequencies. Histologically, PDAC presents as haphazard growth pattern of invasive glands that provoke an intense desmoplastic fibroinflammatory stromal reaction; this robust stromal reaction facilitates tumor cell growth and acts as a significant barrier to effective drug delivery (Feig et al., 2012). PDAC infiltrates along existing duct, nerve and vessel structures to aggressively invade the pancreas and surrounding tissues. Histologic grade is most commonly based on the degree of gland formation, although other criteria (i.e., mitotic activity, nuclear atypia, etc.) have also been proposed as alternatives.

Treatment

PDAC is notoriously resistant to chemotherapy, with only modest survival benefits realized in the adjuvant or neoadjuvant setting. Until recently, single agent chemotherapy (gemcitabine or 5-FU) was the standard chemotherapy regimen employed in either early stage or advanced pancreatic cancer. Radiation therapy has remained a subject of some controversy and its use varies depending on institution. Recent advances include the use of multi-agent cytotoxic chemotherapy, as well as the addition of agents targeting specific molecular pathways (i.e., EGFR inhibition) or the tumor stroma, which have resulted in improved survival outcomes in clinical trials and are now being widely adopted as standard of care for patients able to tolerate these regimens (Paulson et al., 2013).

Prognosis

PDAC accounts for over 220000 annual deaths worldwide, with five year survival for all PDAC patients reported to be 5-6% (Raimondi et al., 2009). Most PDAC patients present with non-operative, locally advanced (AJCC Stage III) or metastatic (AJCC Stage IV) disease. Fewer than 20% of patients present with resectable disease (AJCC Stage I or II). Overall five year survival is still only 15-20% for early stage patients following successful R0 surgical resection, primarily due to metastatic or recurrent local disease (Paulson et al., 2013). This suggests a large percentage of resected patients have clinically unrecognized systemic disease at the time of surgery. Important prognostic factors include initial stage, with significantly improved survival for patients who undergo resection. Factors impacting survival in the setting of resection include margin status, tumor size, histologic grade and lymph node involvement (Hidalgo, 2010).

Genetics

Note

Conventional and molecular cytogenetic analyses of PDAC have demonstrated significant intratumor cytogenetic heterogeneity (ICH), with complex cytogenetic abnormalities and extensive multiclonality. Extensive ICH in PDAC has been shown to correlate with a more dismal prognosis than those with less complex cytogenetic abnormalities (Heim and Mitelman, 2009).

Cytogenetics

Cytogenetics Morphological

Conventional cytogenetic analysis has revealed the following numerical aberrations to be associated with PDAC: -4, -6, +7, -9, +11, -12, -13, -17, -18, +20, -21, -22, -X and -Y. The most common losses in the aforementioned aneuploidies are -18, -17, and -21 and the most common gains are +7 and +20. Balanced and unbalanced structural aberrations revealed by cytogenetic analysis include chromosomal arms 1p, 1q, 3p, 3q, 5p, 6p, 6q, 7q, 8q, 8p, 9p, 11q, 11p, 12p, 15q, 17p, 17q, 18q, 19p, 19q, 20p, and 20q (Heim and Mitelman, 2009).

Cytogenetics Molecular

Molecular cytogenetic techniques most commonly utilized in the analysis of PDAC published in current literature include fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), single nucleotide polymorphism (SNP) arrays, spectral karyotyping (SKY), whole-genome sequencing, etc. CGH analysis applied to malignant PDAC cell lines has

elucidated regions of significant copy number aberrations. Gains of the long arms of chromosomes 11, 8, 3, and 1, as well as losses of 18q, 17p, and 8p were reported to have been the most commonly altered regions. Further analysis showed that the following chromosomal bands/regions were most affected by copy number aberrations: 8q24.2-q24.3, 8q21-qter, 3q23-qter, and 14q11.2-qter (Griffin et al., 2007).

SNP array analyses have revealed significant gains at chromosomal bands 1q21.2-q21.3, 7q36.3, 8q24.3, and 20q13.32-q13.33, as well as significant losses at bands 1p35.3, 9p22.3, 12q23.1, 17p12-p13.3, and 18q21.2. Furthermore, loss of heterozygosity (LOH) has been identified at significant amounts on chromosomal bands spanning 9p21.2-p24.1, 17p11.2-q13.3, and 18q12.1-q12.3 (Gutierrez et al., 2011; Willis et al., 2012). The aforementioned bands are also loci of genes implicated in the genesis of a number of solid-organ and hematological malignancies (for example, CDKN2A and SMAD4).

Genes involved and proteins

Note

A number of genes have been implicated or are suspects in the etiology of PDAC; however, precise diagnostic and prognostic significance has not been established for most, which require further investigation as to their specific roles in pancreatic carcinogenesis and usefulness as prognostic or predictive biomarkers.

Exomic sequencing reveals PDAC tumors average greater than 60 genetic alterations, which includes of a small number of key driver genes mutated at high frequency (KRAS2, TP53, CDKN2A and SMAD4) along with a far larger number of heterogenous genes mutated at lower frequency across the full spectrum of patients (Jones et al., 2008).

KRAS2

Location

12p12.1

Note

KRAS2 mutations have been implicated in > 95% of PDAC. Observed in early PanIN lesions and capable of driving PanIN and PDAC formation in genetically engineered mouse models, oncogenic mutation of KRAS2 is a bona fide early or initiating event for PDAC carcinogenesis (Iacobuzio-Donahue, 2012; Iacobuzio-Donahue et al., 2012). Mutations most commonly occur at codons 12 (54-74%), 13 (3-5%), and 61 (3-5%) (Schultz et al., 2012).

Protein

KRAS2 codes for the ubiquitous RAS protein, which is found on the plasma membrane and mediates GTP-mediated signal transduction pathways involved in cell proliferation, survival and motility, among others.

TP53

Location

17p13.1

Note

TP53 mutations have been implicated in up to 75% of pancreatic cancers and typically arise in later stage PanIN lesions (Iacobuzio-Donahue, 2012; Iacobuzio-Donahue et al., 2012).

Protein

TP53 acts as a tumor suppressor gene and codes for the ubiquitously expressed p53 protein, which acts as multifunctional protein involved in regulating cell cycle progression, senescence, DNA repair and apoptosis.

CDKN2A

Location

9p21.3

Note

CDKN2A inactivation has been implicated in > 95% of pancreatic cancers via a number of mechanisms including genetic deletion and promoter DNA hypermethylation gene silencing.

It is commonly inactivated at an intermediate stage of PanIN progression (Iacobuzio-Donahue, 2012).

Protein

CDKN2A is a tumor suppressor gene that codes for the P16-INK4a protein, which functions to inhibit cell cycle progression at the G1-S checkpoint.

SMAD4

Location

18q21.2

Note

SMAD4 is mutated in up to 55% of pancreatic cancers and typically arise in later stage PanIN lesions or invasive PDAC (Iacobuzio-Donahue, 2012).

SMAD4 inactivation/protein loss is a prognostic marker associated with increased metastatic activity in pancreatic malignancies and thus portends worse prognosis (Iacobuzio-Donahue et al., 2012).

Protein

SMAD4 codes for a namesake protein that is ubiquitously expressed and functions mainly in TGF-beta signaling.

The actions of the Smad4 protein recruit other proteins in the Smad family and synergistically affect transcription by modifying DNA-binding proteins.

ATM

Location

11q22.3

Note

ATM mutations (generally germline mutations) have been implicated in 2.5% of cases of familial pancreatic cancer and 8% of non-familial pancreatic cancer cases

(Iacobuzio-Donahue et al., 2012). ATM has been identified as a prominent susceptibility gene in pancreatic malignancies as well, causing a five-fold increase in the risk of pancreatic cancer development in individuals with ATM aberrations (Roberts and Klein, 2012).

Protein

ATM codes for a protein that is ubiquitously expressed and functions in cell-cycle regulation (checkpoint initiation) by phosphorylating a number of regulatory proteins (for example, p53 and BRCA1).

ATM also functions in DNA repair and damage control associated signaling pathways.

BRCA1

Location

17q21.31

Note

BRCA1 mutations are most attributed to familial pancreatic cancer, and are observed in approximately 3.7% of cases (Iqbal et al., 2012). BRCA1 is considered a susceptibility gene, and aberrations have been observed to increase pancreatic cancer development by 2.2-fold.

The gene has also been a target of PARP inhibitors and DNA cross-linking agents in clinical trials (Roberts and Klein, 2012).

Protein

BRCA1 codes for a ubiquitously expressed namesake protein that functions mainly in DNA repair and damage control, cell-cycle regulation, ubiquitination, transcription regulation, etc. Mutations have been observed to arise via changes to the primary DNA sequence.

Epigenetic events (usually aberrant methylation) can also contribute to its dysregulation.

TGFBR2

Location

3p24.1

Note

TGFBR2 mutations are implicated in 4.1% of pancreatic cancer cases (Goggins et al., 1998). Comprehensive pathway-based analysis of genome-wide association studies finds 43 pancreatic cancer related single-nucleotide polymorphisms (SNPs) in the TGFBR2 gene, and highlights 2 SNPs within the Th1/Th2 immune response pathway (Li et al., 2012).

Protein

TGFBR2 codes for a member of the transmembrane serine/threonine kinase family receptor of TGF- β . TGFBR2 mediates TGF- β cell signaling to regulate cell differentiation and proliferation.

TSC2

Location

16p13.3

Note

Inactivation mutations of TSC2 have been observed in 8.8% of pancreatic neuroendocrine tumor cases (Jiao et al., 2011).

Many signal inputs, such as growth factors, energy availability and Wnt signaling converge with TSC2 to regulate mTOR signaling (Dazert and Hall, 2011).

Loss of tuberin expression by immunohistochemistry has been described to occur in more than 50% of PDAC as well (Kataoka et al., 2005).

Protein

TSC2 codes for a cytoplasmic protein that is widely expressed and is thought to function in GTPase activation and regulation as well as negative regulation of the mTOR pathway.

BRCA2

Location

13q13.1

Note

BRCA2 has been established as a familial pancreatic cancer gene and mutations of it have been observed in 6.1% of cases of familial pancreatic cancer (Iqbal et al., 2012). This gene has been the subject of PARP inhibitors and DNA cross-linking agents, which can potentially provide viable therapeutic agents for pancreatic malignancies (Iacobuzio-Donahue et al., 2012).

Protein

BRCA2 codes for a namesake, ubiquitously expressed nuclear protein and functions mainly in DNA repair and damage control; however, it possesses less major roles in cell-cycle checkpoint and transcription regulation.

PALB2

Location

16p12.2

Note

PALB2 has been reported as a familial pancreatic cancer gene. The truncated PALB2 protein has been observed in 3.1% of familial pancreatic cancer cases (Jones et al., 2009).

Protein

PALB2 is a tumor suppressor gene that codes for a namesake nuclear protein and forms a complex with BRCA1 and BRCA2 which plays an essential role in homologous recombination DNA repair.

PTEN

Location

10q23.31

Note

PTEN mutations are implicated in up to 7.3% of pancreatic neuroendocrine tumor cases and individuals that possess such mutations (as well as mutations in TSC2 (8.8% of cases) and PIK3CA (1.4% of cases))

could potentially be responsive to agents that inhibit the mTOR pathway regulated by the aforementioned genes (Iacobuzio-Donahue et al., 2012). Although PTEN mutations are only rarely detected in PDAC, its loss of function in PDAC has been attributed to a number of other mechanisms including promoter hypermethylation gene silencing and other pathway alterations including changes in AKT expression.

Protein

PTEN codes for a namesake, widely expressed cytoplasmic protein that functions in phosphatase regulation and tumor suppression.

BRAF

Location

7q34

Note

BRAF mutations have been implicated in 16% of PDAC cases (Schultz et al., 2012). In intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, missense mutations within exon 15 have been found in 2.7% cases (Schonleben et al., 2007). So far, no BRAF^{V600E} mutation has been observed in pancreatic cancer.

Protein

BRAF codes for a namesake protein belonging to the raf family of serine/threonine protein kinases. The RAS/BRAF/MEK/ERK pathway functions in cell apoptosis, proliferation and differentiation.

AKT2

Location

19q13.1-q13.2

Note

AKT2 amplification has been implicated in 20% of PDAC samples (Ruggeri et al., 1998). 32-43% of PDAC samples showed a high intensity of AKT2 (Altomare et al., 2002; Yamamoto et al., 2004). Overexpression of AKT2 is sufficient for the metastasis of PDAC (Ruggeri et al., 1998). The mechanisms for AKT2 overexpression in pancreatic cancer involve PTEN loss and/or PI3K activation (Altomare et al., 2002).

Protein

AKT2 codes for a namesake protein belonging to a subfamily of serine/threonine kinases containing SH2-like domains. AKT2 functions to promote cancer cell survival, migration, and invasion. Akt2 is also an important signaling molecule in the insulin signaling pathway.

ARID1A

Location

1p35.3

Note

ARID1A is the likely target of 1p36.11 deletion

observed in pancreatic malignancies (Shain et al., 2012).

ARID1A mutations have been implicated in 8% of pancreatic cancers, including nonsense and indel mutations (Jones et al., 2012).

The internal duplication of ARID1A exons 2-4 in PANC1 cells has been reported (Shain et al., 2012).

Protein

The protein encoded by ARID1A is a key component of the highly conserved SWI-SNF chromatin remodeling complex.

It specifically binds an AT-rich DNA sequence and facilitates transcription.

MLH1

Location

3p21.3

Note

26% of the PDAC showed microsatellite instability (MSI), 23% of which also showed hypermethylation of the promoter of MLH1 (Yamamoto et al., 2001). In another study, the MLH1 hypermethylation rate was 4% in pancreatic carcinomas.

Protein

MLH1 codes for a protein that plays an essential role in DNA mismatch repair along with a set of genes known as mismatch repair genes.

STK11

Location

19p13.3

Note

Germline mutations in the STK11 gene are found in ~70% of Peutz-Jeghers syndrome (PJS) cases (Volikos et al., 2006; Aretz et al., 2005; Chow et al., 2006).

The mutation can be a point mutation or the deletion of parts of the gene. For PJS patients, the cumulative risk for pancreatic cancer is 26% at age of 70 (Korsse et al., 2013).

Protein

Human STK11 encodes for the LKB1 protein that is expressed in all human tissues (Rowan et al., 2000). STK11 is a tumor suppressor gene since it can negatively regulate the activity of mTOR complex 1 (mTORC1) (Dazert and Hall, 2011). STK11 also functions in cell cycle arrest, p53 mediated apoptosis, Wnt signaling and TGF-beta signaling.

To be noted

Note

Some data regarding precise loci, proteins, and functions of the aforementioned genes relevant to pancreas tumors was gathered from the Atlas of Genetics and Cytogenetics in Oncology and Haematology database.

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