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The Mortiferous Transformation-Carcinoma Pancreas

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Abstract

Majority of pancreatic adenocarcinoma are disseminated beyond the anatomical confines of the organ and lymph node metastasis is frequent. On account of rising prevalence and inferior survival rates, cogent screening methodologies are mandated for preliminary detection with enhancing applicability of surgical and medical management. Carcinoma pancreas is commonly discerned beyond fifty five years of age with a predominance betwixt seventh to eighth decade. Pancreatic carcinoma delineates a male predominance with an enhanced incidence in African- American population due to specific risk factors such as cigarette smoking, alcohol intake, elevated body mass index and diabetes mellitus. BRCA1, STK11, PRSS1, CDKN2A and MMR chromosomal mutations can occur within pancreatic adenocarcinoma and familial pancreatic cancer frequently demonstrates genomic mutations such as BRCA2 and PALB. Genetic mutations of pancreatic adenocarcinoma can be assessed with cell free de-oxy ribonucleic acid (DNA) and circulating tumour cells, which can be employed as a screening test. Pancreatic adenocarcinoma and variants are enunciated in a majority (90%) of instances. Low grade Pan IN depict genomic mutations within the KRAS oncogene and a shortening of telomere. Chromosomal mutations of p16, CDNK27, p53 and SMAD4 are contingent to advanced grade of Pan IN and pancreatic adenocarcinoma. Whipple's procedure or a pancreatico-duodenectomy and a distal or total pancreatic resection are suitable options for surgical elimination of pancreatic adenocarcinoma contingent to anatomical tumour localization. Adjuvant chemotherapy or chemo-radiotherapy can augment the percentage of survival.

Keywords: Mortiferous; Pancreatic cancer; Pancreatic Adenocarcinoma

Abbreviations: DNA: De-oxy Ribonucleic Acid; VOC: Volatile Organic Compounds; IPMN: Intra-Ductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm; EGFR: Epidermal Growth Factor Receptor; CEA: Carcino-Embryonic Antigen.

Preface

Pancreatic cancer is a fatal disorder of enhancing incidence demonstrating inferior clinical outcomes. Pancreatic cancer was initially denominated as the fourteenth common cancer and seventh causation of

cancer-associated mortality. During clinical representation, majority of pancreatic adenocarcinoma appear disseminated beyond the anatomical confines of pancreas and are frequently accompanied by lymph node metastasis. As the minimally incident malignancy depicts an inferior survival, assessment of probable factors of disease- emergence is considered essential. On account of rising prevalence and inferior survival rates, employment of cogent screening methodologies are mandated for preliminary detection of a fatal disorder with a consequent enhancement and appropriate application of surgical and medical management. Pancreatic cancer is a terminology which predominantly implies the occurrence of pancreatic ductal adenocarcinoma [1,2].

Disease Characteristics

Recently, enhancing incidence of pancreatic carcinoma is elucidated within the western world equivalently within the genders. At approximately 1.03% current instances per year, carcinoma pancreas is estimated to rank as the second most common factor of cancer-associated mortality within the next decade.

Cogent, modifiable and non-modifiable risk factors for emergence of carcinoma pancreas are exemplified. As carcinoma pancreas is a disorder of the elderly population, majority (90%) of implicated subjects can be discerned beyond fifty five years of age; the malignancy predominates betwixt seventh to eighth decade and is infrequent before thirty years. The neoplasm depicts a male predominance with a male to female ratio at 1.4:1 due to variable environmental and genetic factors. Pancreatic carcinoma delineates an enhanced incidence in the African-American population (50% to 90%), in contrast to Caucasians, which is contingent to specific factors such as cigarette smoking, alcohol intake, elevated body mass index and enunciation of diabetes mellitus. Associated genomic and environmental factors are accountable for diverse ethnicities. Pancreatic adenocarcinoma is associated with variable ABO blood groups. In contrast to blood group O, blood groups A, B and AB demonstrate a markedly enhanced possible emergence of pancreatic adenocarcinoma on account of modifications of glycosyltransferase specificity and altered conditions of host inflammation within various blood groups.

Minimal levels of Neisseria elongate and Streptococcus mitis and elevated Porphyromonas gingivalis and Granulicatella adiacens tend to enhance possible occurrence of pancreatic cancer. Five year survival rate is assessed at 6% and varies from an estimated 2% to 9%. Cogent factors influencing survival are age and gender of individuals, healthcare parameters, occurrence of co-morbid conditions and impact of lifestyle. However, an essential factor implicating subject survival is the specific stage of tumour. As discernment of pancreatic adenocarcinoma is delayed, surgical resection is efficacious in an estimated one fifth (20%) of subjects. A comprehensive and beneficial surgical extermination is accompanied by a five year survival rate of around 27%. However, metastatic pancreatic carcinoma or a locally advanced malignancy demonstrates a median survival of 2 months to 6 months and 6 months to 11 months respectively.

Disease Pathogenesis

Pancreatic carcinoma is contemplated to be of familial occurrence in subjects where two or more first degree relatives are previously discerned with the malignancy and accounts for an estimated 5% to 10% of freshly diagnosed instances. Familial occurrence depicts a nine times enhanced possibility of malignant emergence, in contrast to subjects with no preceding familial incidence. Prevalence is amplified to around thirty times where three or more first degree relatives are discerned with the tumour. Nevertheless, a singular implicated relative elevates the risk of pancreatic adenocarcinoma to nearly 80%.

Familial pancreatic cancer frequently demonstrates genomic mutations such as BRCA2 and PALB. Additionally, BRCA1, STK11, PRSS1, CDKN2A and MMR chromosomal mutations can occur within pancreatic adenocarcinoma. Occurrence of concomitant type 1 and type 2 diabetes mellitus is well established and depicts twice the risk of emerging pancreatic cancer. Also, instances of pancreatic cancer can manifest as new onset diabetes. Assessment of glycosylated haemoglobin (HbA1c) can be employed as a potential biomarker for evaluating diabetes mellitus concurrent with pancreatic adenocarcinoma. Several bacterial and viral infections are concordant with pancreatic carcinoma such as Helicobacter pylori and hepatitis C [2,3].

Preliminary Elucidation of Pancreatic Adenocarcinoma

Cogent biomarkers can be employed for antecedent detection of pancreatic adenocarcinoma. Serum cancer antigen 19-9(CA19-9) can be beneficially adopted for assessment of pancreatic carcinoma. However, on account of a minimal positive predictive value, CA 19-9 is

unsatisfactory for screening of pancreatic adenocarcinoma. It is essentially applied to monitor therapeutic response and as an indicator of reoccurring pancreatic cancer.

Enhanced proportion of genetic mutations associated with pancreatic adenocarcinoma require an assessment of cell free de-oxy ribonucleic acid (DNA)and circulating tumour cells, a manoeuver which can be adopted as a screening or diagnostic test [4,5]. Notwithstanding the amplified KRAS mutations occurring in pancreatic tumour tissue, cell free DNA or circulating tumour cells do not provide adequate sensitivity or specificity to be utilized as a tool for screening.

Mass spectrometry can discern amplified levels of tumour tissue metabolites, particularly in preliminary stages of pancreatic adenocarcinoma. Elevated levels of volatile organic compounds (VOC) in exhaled air specific can be discerned in pancreatic carcinoma. Mutations of deoxyribonucleic acid or mutant p53 can be detected within the pancreatic juice with subjects of pancreatic intraepithelial adenocarcinoma (Pan IN 2-3), intermediate and high grade intra-ductal papillary mucinous neoplasm (IPMN) and invasive pancreatic carcinoma. Next generation sequencing techniques can delineate mutated DNA within the pancreatic juice of individuals with Pan IN, IPMN and invasive cancer, in contrast to healthy adults. A combination of EUS and MRI/MRCP are recommended imaging modalities for delineating pancreatic adenocarcinoma in susceptible individuals. Nevertheless, a validated and cogent biomarker for screening of pancreatic adenocarcinoma is lacking.

Histological Elucidation

Pancreatic adenocarcinoma and cogent variations are enunciated in a majority (90%) instances. Two thirds to three fourths (60% to 70%) instances of pancreatic adenocarcinoma arise within the head of pancreas; nearly 15% instances appear in the body and tail of pancreas respectively. Pancreatic adenocarcinoma usually develops following several genetic mutations for a transformation from a normal, uninvolved mucosal epithelial lining to the emergence of cogent, precursor lesions and an ultimate appearance of an invasive malignancy. Characteristic precursorlesions of pancreatic adenocarcinoma are designated as Pancreatic intraepithelial neoplasia (Pan IN) which is cogitated as a non- invasive, microscopic lesion predominantly occurring in miniature pancreatic ducts beneath <0.5 centimetre in diameter.

Pancreatic intraepithelial neoplasia is incriminated in the emergence of localized pancreatitis. Also, repetitive cycles of epithelial injury and reparative processes can enhance the probable emergence of pancreatic adenocarcinoma. As per contemporary diagnostic criterion, pancreatic intraepithelial neoplasia grade 1a, 1b and grade 2 can be re-classified as low grade pancreatic intraepithelial neoplasia. Similarly, pancreatic intraepithelial neoplasm grade 3 can be re-categorized as a high grade lesion. Pan IN grade 1 demonstrates modifications within a minimal proportion of genes, thus lining duct cells of pancreas are minimally aberrant on morphology. However, intraepithelial pancreatic neoplasm Pan IN grade 2 and 3 are compatible with modifications within several genes and the duct cells depict an augmentation of morphological variations and anomalies. Mutation of KRAS oncogene is prominent, thereby modulating the regulation of cellular growth and progression.

Intra-ductal papillary mucinous neoplasm (IPMN) is a well- delineated precursor lesion of pancreatic adenocarcinoma. The neoplasm can arise from main pancreatic duct or a peripheral branch. Probable transformation into an overt malignancy is variable. An estimated three fourths (70%) malignant conversions can emerge within the main pancreatic duct including carcinoma in situ and around one fourth (25%) mucinous neoplasm appears as a peripheral lesion. Mucinous cystic neoplasm (MCN) is essentially denominated as a premalignant lesion of pancreatic carcinoma and is frequently delineated in female subjects. Mucinous neoplasm appear in around one fourth (25%) of pancreatic cysts subjected to a comprehensive surgical resection. Nearly 1% of computerized tomography scans of the abdomen can discern a cystic lesion of pancreas.

Molecular Modifications

Intraepithelial pancreatic neoplasm is a frequent precursor of pancreatic adenocarcinoma and cogent histological transformation is concordant to accumulation of chromosomal aberrations. Inherent modifications within the genetic components such as BRCA2, p16 and genes contingent to Lynch syndrome enhances probable emergence of pancreatic cancer. Low grade Pan IN depicts genomic mutations within the KRAS oncogene and exhibit cogent shortening of the telomere as a component of preliminary modifications of invasive malignancy. Chromosomal mutations of p16, CDNK27, p53 and SMAD4 are contingent to advanced grade of Pan IN and pancreatic adenocarcinoma [5,6]. Proportion of KRAS mutations is enhanced and concurrent to grading of Pan

IN. Anomalies of notch signalling pathway and sonic hedgehog pathway are incriminated although a majority (80%) of chromosomal mutations are sporadic. Pancreatic adenocarcinoma demonstrates repetitive chromosomal mutations in approximately thirty two genes which are further sub-categorized as squamous, pancreatic progenitor, immunogenic and aberrantly differentiated endocrine exocrine gene. Each subgroup has a unique genomic signature which is concordant to morphological picture and prognostic outcomes.

Squamous subtype of chromosomal mutation is concurrent with adeno-squamous histological variant [5,6].Pancreatic progenitor genomic sub-category demonstrates prominent enunciation of transcription factors which determine pancreatic cell lineage. Prominent immune infiltration is observed in immunogenic variant of pancreatic adenocarcinoma. Aberrantly differentiated endocrine exocrine tumours commonly depict predominant acinar cell differentiation. Also, majority of pancreatic tumours exemplify androgen receptors, a feature which can be beneficially employed for administering targeted chemotherapy [6,7].

Therapeutic Options

Surgical resection is considered an optimal procedure for treating pancreatic adenocarcinoma. Adoption of adjuvant chemotherapy or chemo-radiotherapy can augment the percentage of survival. Whipple's procedure or a pancreatico-duodenectomy and a distal or total pancreatic resection can be contemplated as suitable options for surgical elimination of pancreatic adenocarcinoma and can be adopted contingent to anatomical location of the tumour.

Neoadjuvant therapy and vascular resection is employed to enhance microscopic clearance of the tumour. Microscopic clearance is defined as microscopic evidence of cancerous cells emerging at the perimeter of surgical resection or appearance of tumour within one millimetre of the resection margin. Pre-operative biliary drainage is adopted for pancreatic adenocarcinoma which represent with jaundice. Notwithstanding, the procedure may or may not be advantageous. Enhanced percentage of peri-operative complications can be encountered with biliary drainage [7,8].

Minimally invasive, laproscopic surgery or distal pancreatectomy can be adopted to treat pancreatic adenocarcinoma. The procedure is associated with reduced blood loss and a decline in hospital stay. Laproscopic distal pancreatectomy is the initial pancreatic procedure to be successfully adopted as a therapeutic option. However, proportion of tumour occurrence within the resection margin is identical as cogitated with open or laproscopic procedures. Vascular resection of surrounding vasculature is accompanied by increased perioperative mortality and inferior procedural outcomes, as enunciated at one and three years following arterial reconstruction. Tumour infiltration of the celiac trunk and superior mesenteric artery is considered as a contraindication to vascular resection. Also, advantage of vascular resection as a procedure in pancreatic cancer infiltrating the portal and mesenteric vessels is debatable [7,8] (Figures 1-8).

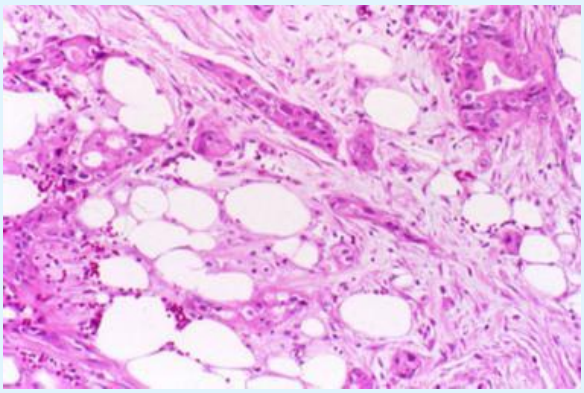

Figure 1: Carcinoma pancreas with glandular configuration, nuclear hyperplasia, hyperchromasia, anisonucleosis and tumour associated desmoplasia [9].

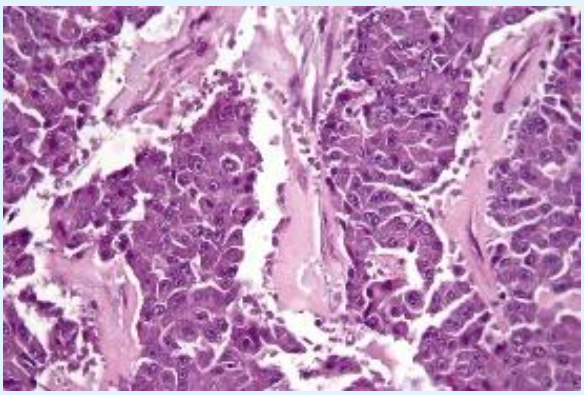

Figure 2: Acinar carcinoma pancreas with foci of glandular differentiation, uniform cells with abundant eosinophilic cytoplasm, atypical basal nuclei and minimal stroma [10].

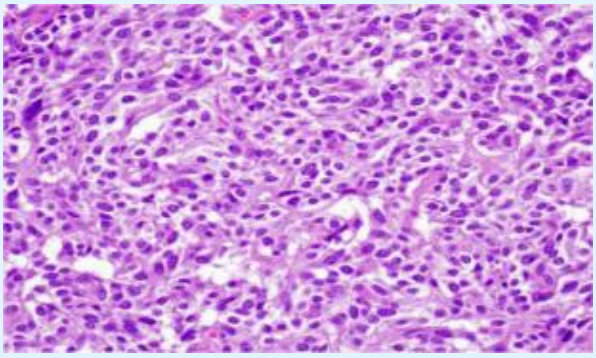

Figure 3: Carcinoma pancreas with neuro-ectodermal differentiation with miniature round cells, scant cytoplasm, uniform nuclei and a circumscribing fibro-vascular stroma [11].

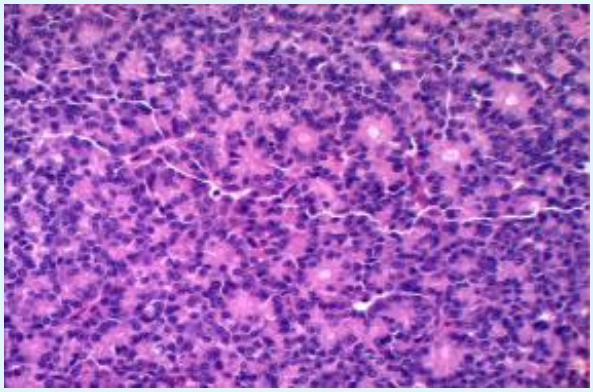

Figure 4: Acinar carcinoma pancreas with solid sheets and glandular pattern of tumour cells with abundant eosinophilic cytoplasm, scanty stroma and absent desmoplasia [11].

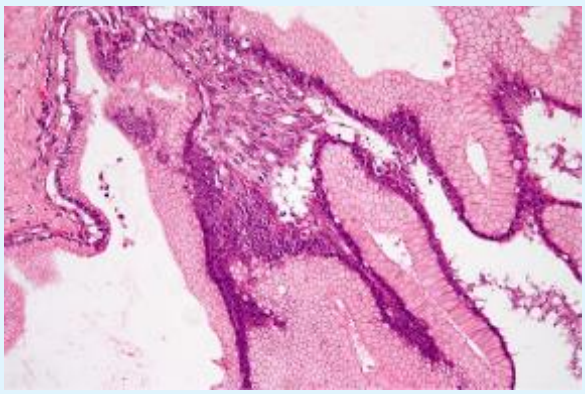

Figure 5: Mucinous cystic variant of carcinoma pancreas with inner epithelial layer, outer densely cellular mullerian layer and mucin secretion [11].

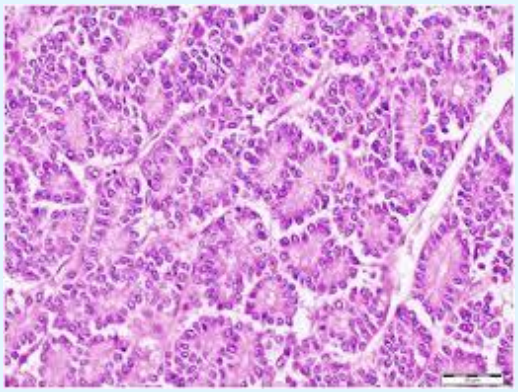

Figure 6: Carcinoma pancreases with neuro-ectodermal differentiation with small, round, uniform cells, glandular configuration and enveloping fibro-vascular stroma [12].

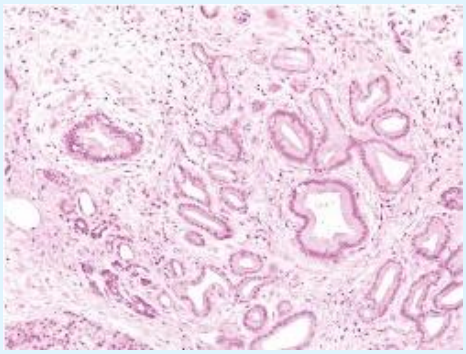

Figure 7: Carcinoma pancreas with acini and neoplastic glandular structures with nuclear hyperplasia, hyperchromasia, anisonucleosis, mucin secretion and minimal desmoplasia [13].

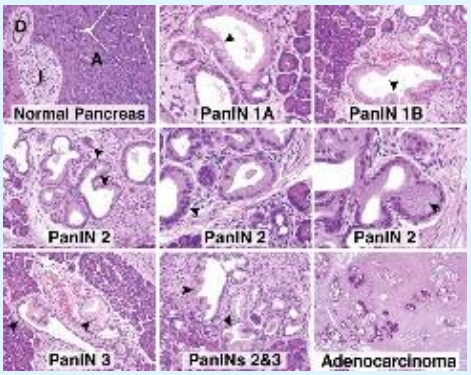

Figure 8: Carcinoma pancreases with transition between various stages of normal pancreas, grades of pancreatic intraepithelial neoplasm and frank adenocarcinoma [14].

Adjuvant chemotherapy with gemicitabine following comprehensive surgical resection demonstrates an enhanced median disease free survival and overall survival at five and ten year interval. Gemcitabine is considered as a preferred therapeutic agent, in contrast to 5 fluorouracil. Combination therapy of gemcitabine and capecitabine is advantageous in locally advancedor metastatic pancreatic cancer. Administration of m FOLFIRONOX, which is essentially a combination of oxaliplatin, irinotecan and leucovorin, demonstrates a significantly superior disease free survival and overall survival. However, therapeutic complications are also enhanced with the adoption of aforesaid agents. Neoadjuvant therapy provides a distinct survival benefit. Nevertheless, despite the application of neoadjuvant treatment, an estimated three fourths (71% to 76%) of subjects depict a malignant relapse within two years.As surgery associated complications are encountered in around 40% individuals; neoadjuvant chemotherapy cannot be concurrently employed. Neo-adjuvant chemotherapy is associated with an advantage of eliminating micro-metastasis and shrivelling of primary tumour accompanied by a declining incidence of tumour reoccurrence [7,8]. Complications of neoadjuvant chemotherapy can delay or prevent a surgical procedure. The malignancy can also be unresponsive to neoadjuvant chemotherapy or radiotherapy and previously resectable cancers can convert into non-resectable tumours. Chemo-radiotherapy induced fibrosis within the pancreatic tissue enhances the proportion of complications following pancreatectomy.

Neoadjuvant chemotherapy can be satisfactorily employed for managing resectable or borderline disease. Resectable disease is defined as an absence of tumour incrimination of superior mesenteric artery, portal vein, coeliac axis or superior mesenteric vein. Borderline resectable disease is designated as the degree of tumour implication of aforementioned major vascular structures [7,8]. Targeted therapy is applicable in cogent variants of pancreatic adenocarcinoma. Cancer cells display specific surface proteins cogitated as growth factor receptors such as epidermal growth factor receptor (EGFR) which can be targeted with pertinent chemotherapeutic agents. Thus, erlotinib can be efficaciously combined with gemcitabine.

Anti angiogenesis factors or drugs are suitable in curtailing the emergence of newly formed blood vessels with a consequent declination of malignant cells. Immune therapy can beneficially augment individual immune system or contribute towards prepared constituents of immune system in order to invade malignant cells [7,8]. Monoclonal antibodies are pertinent, injectable immune system proteins which can concentrate into specific molecules such as carcino-embryonic antigen (CEA) and are located upon the extraneous surface of pancreatic cancer cells. The chief function of monoclonal antibodies is to decimate carcinoma cells and abstain from destruction of normal cells.

Cancer vaccines are employed to augment the immune response of an individual. In contrast to vaccines countering pertinent infections, cancer vaccines are designed to therapeutically alleviate malignancies such as pancreatic cancer. Aforesaid vaccines are associated with minimal side effects [1,2]. Novel agents who target immune checkpoint system can be efficaciously employed to exterminate pancreatic adenocarcinoma. Immune system usually circumvents an invasion against self by the enunciation of immune checkpoint-proteins situated upon immune cells which necessitate an activation and/or inactivation in order to cultivate an adequate immune response. Cancer cells can specifically adopt mechanisms to utilize cogent checkpoints in order to prevent an attack from the native immune system [1,2].

Individualization of pertinent therapeutic options can be advantageous in specific subjects such as the employment of erlotinib in pancreatic carcinoma which delineates modifications within the EGFR gene. Apropos genetic alterations within the tumour can also modify therapeutic outcomes with gemcitabine. Metastasis of pancreatic adenocarcinoma requires the curtailment of systemic symptoms, management of jaundice and administration of palliative chemotherapy, preferably with m FOLFIRONOX in combination with 5 fluorouracil [1,2] (Tables 1 &2).

Risk Factor	Disease Implications	Specific Findings
Smoking	Enhanced possibility 74% risk in current smokers, 20% risk in previous smokers	Dose-responsive, risk persists up to 10-20 years following smoking cessation
Alcohol	Variable, 15%-43% increased risk	Dose-responsive, gender predilection, possibility in chronic pancreatitis
Obesity	10% enhanced risk with augmentation of 5 BMI units each	Associated with type 2 diabetes mellitus, risk factor for pancreatic carcinoma

Dietary Factors	Variable, augmented risk with enhanced intake of red meat	Consensus unavailable, requires extended evaluation
Helicobacter pylori	45% enhanced risk	Further evaluation

Table 1: Modifiable risk factors associated with pancreatic carcinoma [1].

Morphological Variants	Microscopic Characteristics
Adeno-squamous carcinoma	Prominent components of ductal/glandular and squamous differentiation (30%). Inferior prognosis
Colloid/ Mucinous carcinoma	Configuration of copious, extracellular stromal mucin. Majority arise in association with in intra-ductal papillary mucinous neoplasm. Favourable prognosis.
Undifferentiated/ Anaplastic carcinoma	Markedly atypical cells with minimal or absent differentiation. Spindle or sarcomatoid cells admixed with osteoclast-like giant cells. Aggressive neoplasm. Poor prognosis.
Signet ring cell carcinoma	Dissemination of single cells with intra-cytoplasmic mucin. Identical tumours throughout GIT. Poor prognosis.
Medullary carcinoma	Syncytial arrangement of pleomorphic epithelial cells with accompanying intra-tumoural lymphoid infiltrate. Slightly superior prognosis.
Hepatoid carcinoma	Similar to hepatocellular carcinoma, may produce bile. Rare tumour with poor prognosis.

Table 2: Subtypes of pancreatic ductal adenocarcinoma [1].

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9. Image 1 Courtesy: Medscape

10. Image 3 Courtesy: Wikipedia

11. Image 2, 4 and 5 Courtesy: Translational Cancer Research

12. Image 6 Courtesy: Wiley Online Library.

13. Image 7 Courtesy: Baishideng Publishing Group.

14. Image 8 Courtesy: Journal of Immunology.