Pancreatic cancer

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Abstract

It is anticipated that by 2030 pancreatic cancer will be the second leading cause of death from cancer. Surgery remains the only potentially curative therapy. However, less than a quarter of patients are suitable for surgical resection. The lack of early symptoms, the propensity for pancreatic cancer cells to metastasize early in disease development together with the marked resistance to chemotherapy and radiotherapy, are partly responsible for the poor survival rates. Recent improvements in diagnostic imaging, such as pancreas protocol computed tomography and the role of endoscopic ultrasound, allow for earlier detection and facilitate earlier management of pancreatic cancer. In recent years, the approved use of FOLFIRINOX and gemcitabine nab-paclitaxel regimens in patients with metastatic disease has seen an improvement in survival rates and there has been increasing interest in its use in neoadjuvant chemotherapy. Future perspectives include studying the carcinogenesis of pancreatic malignancy and tumour-related genetic mutations, which it is hoped will lead to new developments in the management of pancreatic cancer, and indeed in survival rates.

Keywords Chemotherapy; genetic mutation; neoadjuvant treatment; palliative care; pancreas cancer; pancreatic ductal adenocarcinoma; surgery

Introduction

For the majority of patients diagnosed with pancreatic cancer it remains a lethal disease. Currently it is the fourth leading cause of cancer-related death in Europe and the United States.[1] Pancreatic cancer accounts for 2.5% of all invasive cancers in Ireland and is the 11th most common cancer with 478 new cases diagnosed in 2012.[2] It is the fifth most common cause of invasive cancer death, with 478 deaths per year. Pancreatic cancer is predominantly a disease of the elderly, occurring mainly between the seventh and eighth decade, with the risk increasing with age. It rarely affects individuals younger than 45 years of age. In common with other Western countries the majority of patients present with advanced disease.

The annual incidence of pancreatic cancer is rising with approximately 48,960 new cases and nearly 40,560 deaths estimated in 2015 in the United States, with an overall 5-year survival rate of 7.2%.[3] In the UK, the incidence of pancreatic cancer has been reported to be 15.7 per 100,000 population per year, with a mortality rate of 9.1 per 100,000 and a 5-year survival rate of 3.3%.[4] Without any substantive improvement in curative therapies, pancreatic cancer is anticipated to be second leading cause of deaths in 2030.[1]

Complete surgical resection remains the only treatment that can provide prolonged survival. However, the majority of patients have advanced disease at presentation.

Recently, increased awareness, improved understanding of the pathogenesis of the disease, enhanced diagnostics and the development of more effective chemotherapeutic strategies have led to a sense that new therapeutic opportunities in pancreatic cancer may be soon available.[5]

This article reviews these developments.

Aetiology

Pancreatic ductal adenocarcinoma accounts for the majority of malignant pancreatic diseases. A number of aetiological variables have been identified. The major environmental factor appears to be smoking. Obesity has also been implicated. It is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation and altered secretion of adipokines, all of which are involved in carcinogenesis and cancer progression.[5]

Long-standing type 2 diabetes mellitus also appears to be associated with increased pancreatic cancer risk. In contrast, diabetes mellitus of recent onset (<2–3 years) is rather considered as an early para-neoplastic manifestation, caused by paracrine cancer-induced β-cell dysfunction and peripheral insulin resistance and probably is not an aetiological factor.

Patients with chronic pancreatitis have an increased risk of developing pancreatic cancer. Despite the elevated risk, screening in patients with non-hereditary chronic pancreatitis is not recommended because the absolute risk is limited (4% after 20 years of evolution) and tumour detection by imaging is challenging in a remodelled parenchyma.

Others factors have been suggested to increase pancreatic cancer risk such as non-O blood group, *Helicobacter pylori* infection and chronic hepatitis B or C infection, but further studies are needed to confirm these associations.

Finally, a familial history of pancreatic cancer is present in 7–10% of patients. Following the International Cancer of the Pancreas Screening Guidelines published in 2012, individuals with at least two blood relatives with pancreatic cancer, with at least one affected first-degree relative and absence of the criteria for other inherited tumour syndromes associated with increased risk of pancreatic cancer, should be considered for screening.

Pathology and pathogenesis

Pancreatic ductal adenocarcinoma arises from a series of progressive genetic mutations and specific precursor lesions, such a mucinous cystic neoplasm, pancreatic intraepithelial neoplasm (PanIN) and intraductal papillary mucinous neoplasms (IPMN).

Genetic

Germ line and somatic mutations contribute to the development of pancreatic cancer. It is becoming clear that pancreatic cancer tumours are highly heterogeneous showing that tumours contain

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an average of 63 genetic alterations. This heterogeneity may partially explain the resistance of pancreatic cancer to chemotherapy.

Over 90% of patients with pancreatic cancer possess mutations in the k-ras oncogene which is mutated in 20–30% of all human malignancies. Mutations within this oncogene are most often located on exon 1 of codon 12 and sometimes on codons 61 and 13. k-ras seems to appear in early stages of pancreatic carcinogenesis, but accumulation of other cooperative genetic alterations is required for full oncogenic transformation.[2]

The most recognized tumour suppressor gene implicated in pancreatic cancer development (p53) is found in over 75% of specimens mutated. SMAD4 inactivation is a late event present in 50–60% of cases and may be associated with more aggressive disease.[1] Others tumour suppressor genes include DPC4 (deleted in Pancreatic Cancer, locus 4), LKB1 (liver kinase B1), MAPK (mitogen activated protein kinase), BRCA2 and CDKN2A.

Global genomic analyses have provided a new insight into pancreatic cancer genetic complexity. Recently, studies using whole-exome sequencing and copy number analysis have uncovered novel mutated genes including genes involved in chromatin modification (EPC1 and ARID2), DNA damage repair (ATM), axon guidance (SLIT/ROBO) and other mechanisms.[6]

Further studies will determine whether these mutations affect oncological outcomes and if this tumour microenvironment could represent a therapeutic target.

Pre-malignant lesions

Pancreatic intraepithelial neoplasms (PanIN) are microscopic (<0.5 cm), non-invasive epithelial proliferations within the pancreatic ducts. The process preceding PanIN formation is also known as acinar-to-ductal metaplasia. Following pancreatic injury or k-ras activation, acinar cells gradually lose their acinar features and acquire ductal phenotype 17. These lesions are classified into four grades (PanIN-1A, -1B, -2 and -3) depending of increasing dysplasia in parallel with the accumulation of mutations (Figure 1).

Intraductal papillary mucinous neoplasm (IPMN) is the second major pancreatic cancer precursor lesion after PanIN. IPMNs are a heterogeneous group of cystic macroscopic lesions that can arise from the main or branch pancreatic ducts. These tumours often produce large amounts of mucin leading to ductal dilatation and occasionally pancreatitis as the result of the obstruction of the pancreatic duct. The 5-year risk of pancreatic cancer has been estimated at 10–15% for branch duct IPMN and exceeds 50% in cases of main duct IPMN.[7]

Four histologic subtypes have been described (gastric, intestinal, pancreatobiliary, and oncocytic). Branch duct IPMNs are mainly of the gastric phenotype. The intestinal type is mostly seen in main duct IPMN progressing into invasive cancer of colloid or tubular type. International consensus guidelines for the management of IPMN are shown in Figure 2.

Mucinous cystic neoplasms (MCN) are large mucin-producing pre-malignant lesions of the pancreas arising mostly in the body or tail of the gland. The median age at diagnosis is 40–50 years and almost exclusively in women. MCNs are not connected with the pancreatic duct, typically are unique, unilocular or paucilocular cysts with few septations. They usually display a thick wall (>2 mm) and are surrounded by a pathognomonic ovarian-type stroma. The presence of mural nodules, a thick wall and a

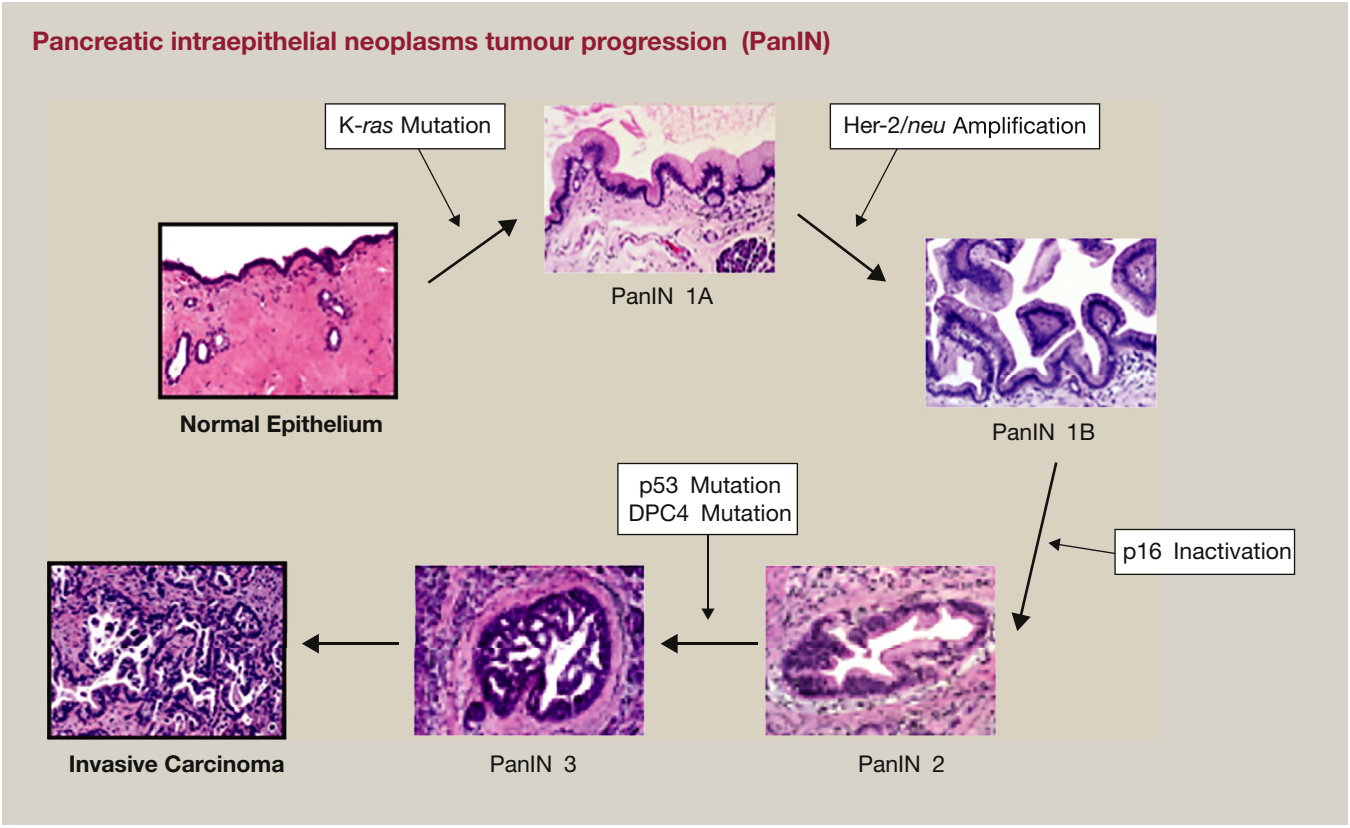

Figure 1