Pancreatic cancer

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Abstract

The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma. The long-term outcome of pancreatic cancer is extremely poor, the overall median survival from diagnosis being 3–6 months without treatment, which increases to around 23 months with resectional surgery and adjuvant treatment. Pancreatic cancer is usually diagnosed late and has a biological phenotype characterized by resistance to all cancer treatment modalities and early metastasis. Jaundice is the most common presenting symptom. Endoscopic stent placement is preferable to transhepatic stenting. The average patency of metal biliary stents is about twice that of plastic stents, the latter lasting about 4 months. Curative surgery is rare. Pancreatoduodenectomy is the most appropriate resectional procedure for tumours of the head of the pancreas. The operation should be confined to specialist centres to reduce morbidity and mortality and increase resection rates. Adjuvant treatment is recommended for those who undergo resection with curative intent. Efforts should be made to obtain a tissue diagnosis in patients selected for palliation. In the event of gastric outlet obstruction, endoscopic duodenal stenting should be used in addition to palliative endoscopic biliary stenting. If chemotherapy is used for palliation, the combination chemotherapy regimen of FOLFIRINOX is currently the treatment of choice.

Keywords Chemotherapy; palliative care; pancreatic cancer; radiation therapy; surgery

What's new?

- The relative risk of patients with first-degree relatives diagnosed with pancreatic cancer as compared to the general population is increased 2-, 6- and 30-fold in those with one, two and three affected family members, respectively
- The most common precursor to pancreatic cancer is known as pancreatic intraepithelial neoplasia (PanIN). These are microscopic and demonstrate a stepwise progression from low to high grade in types 1, 2, and 3, each type accumulating clonally selected genetic and epigenetic mutations as they progress
- Advances in operative techniques and technology have led to an increase in the number of laparoscopic pancreatic resections being performed
- Adjuvant treatment is recommended for those who undergo pancreatic resection with curative intent
- It is now recommended that the combination chemotherapy regimen of oxaliplatin, irinotecan, FU and leucovorin (FOLFIRINOX) is the first-line treatment for patients with metastatic pancreatic cancer with a good performance status

The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma. It has the highest ratio of diagnosis to mortality of all pancreatic tumours. The overall median survival from diagnosis is 3–6 months without treatment, but increases to around 23 months after resectional surgery and adjuvant treatment.[1] Pancreatic cancer is usually diagnosed late and has a biological phenotype characterized by resistance to all cancer treatment modalities and early metastasis. Curative surgery is rare and requires specialized expertise found in a limited number of centres.

Epidemiology

In the UK and the USA, the annual incidence of pancreatic cancer is approximately 100 per million population; it is the fourth most common cancer resulting in death in these countries.[2,3] The incidence is higher in Western or industrialized countries in general. The disease is rare before the age of 45 years, and approximately 80% of cases occur between 60 and 80 years of age. Throughout the world, pancreatic cancer is more common in men than women, with a male-to-female ratio of between 1.5 and 2, but recent figures from the UK suggest that this male preponderance has declined in the last two decades to 1.25:1.[4]

Aetiology

Several risk factors have been identified, the most established being cigarette smoking which may account for approximately 25–30% of cases.[5] Patients with chronic pancreatitis have an up to 18-fold higher risk, and there is a relative risk of 1.8 in people with type 2 diabetes mellitus compared with the general population. Data on the effects of other diseases, such as cholelithiasis, previous gastric surgery and pernicious anaemia, are considered weak overall. Other potential factors that have been examined in detail include diet (high fat and protein, low fruit and vegetable intake), coffee consumption, alcohol and occupational exposure (to insecticides, aluminium, nickel or acylamide), although data are not robust. Hereditary pancreatitis (HP) is associated with a 50- to 70-fold risk and a cumulative lifetime risk to the age of 75 years of 40%.[6] Mutations of the genes *PRSS1*, *SPINK1* and *CFTR* are those most commonly linked to HP. An increased risk of pancreatic cancer may occur as part of other familial cancer syndromes, including familial atypical multiple mole melanoma (mutation of the tumour suppressor gene *p16*), Peutz–Jeghers syndrome (mutation of the tumour suppressor gene *STK11*), hereditary non-polyposis colon cancer (Lynch syndrome) (mutations of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*), familial breast–ovarian cancer syndromes (*BRCA1*, *BRCA2* and *PALB*) and familial adenomatous polyposis (mutation of the tumour suppressor gene *APC*). A family history of pancreatic cancer is an important risk factor, about 7–10% of affected patients having a family history. The relative risk of patients with first-degree relatives diagnosed with pancreatic cancer as

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compared to the general population is increased 2-, 6- and 30-fold in those with one, two and three affected family members, respectively.[7]

Pathology

Ductal adenocarcinomas of the pancreas account for more than 85% of all exocrine pancreatic tumours. They evolve via microscopic premalignant pancreatic lesions associated with pancreatic ducts, known as pancreatic intraepithelial neoplasias (PanIN). There is a stepwise progression of PanIN from low to high grade in types 1, 2 and 3, each type accumulating clonally selected genetic and epigenetic mutations as it progresses. It has been estimated that a precursor neoplastic clone takes more than 10 years to evolve into a malignant clone and then several additional years for metastatic subclones to emerge.[8] Morphological variants (giant cell carcinoma, adenosquamous carcinoma and mucinous carcinoma) and acinar cell carcinoma all have similar or worse prognoses than ductal adenocarcinoma. Pancreatic cancer has a propensity for perineural invasion within and beyond the gland, for vascular invasion, and for rapid lymphatic spread. The most common sites for extra-lymphatic involvement are the liver, peritoneum and lung. Several other exocrine tumours arise from the pancreas, most of which — including mucinous tumours, intra-ductal papillary mucinous neoplasms (IPMN), and solid-pseudopapillary tumours — carry a better prognosis than pancreatic ductal adenocarcinoma.

Clinical presentation

Trousseau's sign of migratory thrombophlebitis or venous thromboembolism has been reported in 7% of patients with pancreatic cancer, especially those in the body and tail. Virchow's node (left supraclavicular lymph node) and Sister Mary Joseph nodule (umbilical metastatic lesion) are also well-described features of advanced disease. Some 5% of patients with pancreatic cancer will have developed diabetes mellitus within the previous 2 years, and many more have impaired glucose tolerance.

Carcinoma of the head of the pancreas

At least two-thirds of pancreatic cancers arise in the head of the gland.

- Jaundice is present in over 90% of patients as a result of either invasion or compression of the common bile duct. The jaundice is often painless but tends to be progressive and is usually accompanied by pruritus.
- Weight loss may be prominent and occurs as a result of anorexia, malabsorption (secondary to exocrine insufficiency) and diabetes.
- Pain is present in about 70% of patients at the time of diagnosis and is usually located in the epigastrium or left upper quadrant. It is often vague in nature and radiates to the back in 25% of patients. Back pain usually indicates posterior capsule invasion and unresectability.
- Five per cent present with an atypical attack of acute pancreatitis.
- In advanced cases, duodenal obstruction results in persistent vomiting.
- Another late manifestation is gastrointestinal bleeding as a result of either duodenal invasion or varices secondary to portal or splenic vein occlusion.
- A palpable gallbladder (Courvoisier's sign) is commonly found in jaundiced patients with malignant obstruction of the lower common bile duct (as opposed to ductal stones).

Carcinoma of the body and tail of the pancreas

These tumours develop insidiously and are asymptomatic in their early stages. At diagnosis they are often more advanced than lesions located in the head. There is marked weight loss with back pain in 60% of patients. Jaundice is uncommon and usually reflects advanced cancer with involvement of the porta hepatis. Vomiting sometimes occurs at a late stage from invasion of the duodenojejunal flexure. An abdominal mass is detected more often than in cancer of the head of the pancreas and indicates unresectability. Indeed, most cancers outside the head of the pancreas are beyond the realms of surgical cure at the time of diagnosis, because of either liver metastases or local invasion of the coeliac axis and superior mesenteric vessels.

Investigations

The investigation of patients with suspected pancreatic cancer should focus initially on establishment of the diagnosis and an assessment of the patient's fitness to undergo potentially curative treatment.

- The most valuable tumour marker is carbohydrate antigen 19-9 (CA19-9; normal range 0—37 U/ml). A falsely elevated CA19-9 concentration may occur in non-malignant conditions such as pancreatitis, hepatic dysfunction and obstructive jaundice. Concentrations higher than 200 U/ml confer 90% sensitivity, whereas concentrations in the thousands are associated with high specificity.
- Initially, the preferred radiological investigation is ultrasonography, which can identify pancreatic tumours, dilated bile ducts and liver metastases.
- Dual-phase spiral computed tomography (CT) accurately predicts resectability in 80—90% of cases. CT features of unresectability include contiguous organ or vascular invasion, including the superior mesenteric and portal vein, coeliac axis and superior mesenteric artery, and distant metastases (Figure 1).
- Magnetic resonance (MR) imaging detects and predicts resectability with accuracies similar to CT. MR cholangiopancreatography (MRCP) provides detailed ductal images without risking the complications incurred by endoscopic retrograde cholangiopancreatography (ERCP).
- ERCP can confirm the typical 'double duct' sign (adjacent strictures in the bile duct and main pancreatic duct) and provides the opportunity for aspiration or brushing of the bile-duct system. It also offers a therapeutic modality, namely biliary stenting to relieve jaundice.
- Endoscopic ultrasonography (EUS) is highly sensitive in the detection of small tumours that are equivocal on CT, assessing vascular invasion, and provides a further opportunity for biopsy or fine-needle aspiration.
- Positron emission tomography (PET) is mainly used for demonstrating occult metastases, although it is important to remember that hyperglycaemia may result in false negatives.