

# Multidisciplinary Symposium — Carcinoma of the Pancreas

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## The surgeon's view

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### Introduction

Pancreatic cancer remains a deadly disease in which the incidence and mortality are identical. Few patients survive, and the long-term surgical survivors are prone to recurrence, even 10–15 years later. The incidence of pancreatic cancer has remained static for the last decade with male and female incidence being similar; approximately 10 new cases occur per 100 000 population per annum. The recent trend has been for the disease to occur in older age groups and now in the UK 50% of patients are over 75 years of age. Risk factors are few and the aetiology appears multifactorial; smoking appears the most important, with chronic pancreatitis, hereditary predisposition, diabetes and carcinogens being of importance. Approximately 90% of tumours are ductal carcinomas with the remaining 10% being a wide range of different tumour types with a remarkably variable prognosis. The importance of defining the histology is probably of greater importance in pancreatic cancer than in most other tumours. Characteristically, tumours present late.

### Symptoms and signs

The suspicion of pancreatic cancer arises because of symptoms such as pain, jaundice, weight loss, anorexia or early satiety. Less common symptoms include venous thrombosis, diarrhoea, new onset diabetes or acute pancreatitis. Back pain is ominous and associated with a shortened survival. Painless jaundice is the most common presentation in patients with a potentially resectable and curable lesion (52% of patients with a resectable lesion). Pain, however, is the most frequent symptom and is present in 80% and 85% of patients with locally unresectable and advanced cancer, respectively. The combination of pain and jaundice is present in 50% of patients with a locally unresectable tumour.

In a prospective study of 39 patients with unresectable pancreatic cancer, 82% had pain at the time of diagnosis, 64% anorexia, 62% early satiety, 54% sleep problems,

and 51% weight loss. Significant correlation has been found between dyspnoea and length of survival.

### Pathology

Currently there are two major classifications; the TNM created by the UICC and a Japanese system (JPN) created by the Japan Pancreas Society. UICC is based on tumour size and the presence or absence of nodal or remote metastases, whereas the JPN classification has more criteria; for example, a more detailed evaluation of the degree of invasion into vessels, retroperitoneum and nerves. Evaluation of the remote nodal, as well as the hepatic and peritoneal metastases is more neatly differentiated. For individual tumours, the WHO classification<sup>[1]</sup> groups the exocrine tumours according to their biological behaviour. The division between benign and malignant is not sharp, but rather a gradual transition analogous to some ovarian tumours. The borderline group, known as 'tumours of uncertain malignant potential' are defined by the grade of dysplasia and their potential to become malignant. In the 1996 edition of the classification, a new name 'intraductal papillary mucinous tumour' replaced vague terms such as 'mucin-producing tumour', 'mucinous duct ectasia' and 'solid pseudopapillary tumour' (Table 1). Ductal adenocarcinomas compose 90% of pancreatic tumours. Sixty-five per cent of these tumours arise in the head of the pancreas, 15% originate in the body and tail, and 20% diffusely involve the gland. The tumour infiltrates and creates a fibrous response such that the extent is difficult to appreciate and indeed, microscopically, extends significantly beyond the grossly recognized tumour mass. At the time of presentation most tumours have metastasized to the lymph nodes, and later extend to the liver (80%), peritoneum (60%), lungs and pleura (50–70%), and the adrenal glands (25%). Most ductal adenocarcinomas infiltrate the perineural, lymphatic and vascular channels.

Endocrine pancreatic tumours arise from the diffuse endocrine system (DES), the cells of which share a

**Table 1 WHO classification of exocrine pancreatic tumours**

Benign tumours
Serous cystadenoma
Mucinous cystadenoma
Intraductal papillary-mucinous adenoma
Mature teratoma
Borderline tumours (uncertain malignant potential)
Mucinous cystic tumour with moderate dysplasia
Intraductal papillary-mucinous tumour with moderate dysplasia
Solid-pseudopapillary tumour
Malignant
Severe ductal dysplasia — carcinoma <i>in situ</i>
Ductal adenocarcinoma
Mucinous non-cystic carcinoma
Signet ring carcinoma
Adenosquamous carcinoma
Undifferentiated (anaplastic) carcinoma
Mixed ductal-endocrine carcinoma
Osteoclast-like giant cell tumour
Serous cystadenocarcinoma
Mucinous cystadenocarcinoma
Noninvasive
Invasive
Intraductal papillary-mucinous carcinoma
Noninvasive
Invasive (papillary-mucinous carcinoma)
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Mixed acinar-endocrine carcinoma
Pancreatoblastoma
Solid-pseudopapillary carcinoma
Miscellaneous carcinomas

number of antigens with nerve elements, hence the name 'neuroendocrine'. The importance of these tumours is that the relatively benign and differentiated tumours give rise to systemic endocrine syndromes (insulinoma, gastrinoma, glucagonoma, VIPoma, PPoma), while the more malignant and non-hormone-producing tumours grow slowly and have a longer life-cycle than the ductal cancer. Similarly, ampullary tumours have different behavioural patterns and present early due to obstruction of the ampulla of Vater; their prognosis is similar to colonic tumours. It is important to characterize precisely the pancreatic tumour in order to define a treatment plan and consider prognosis.

## Diagnosis

The therapeutic advantages of an early, accurate and precise diagnosis are obvious and indicate the need for standards for history-taking and physical examination as well as non-invasive, highly sensitive and specific methods of investigation. The diagnosis of carcinoma in the head of the pancreas can be made in 90% of patients on the basis of clinical presentation. In a study of 356 patients with pancreatobiliary carcinoma, the clinical and diagnostic tests reviewed showed that percutaneous

transhepatic cholangiography (PTC) and computed tomography (CT) scanning were associated with the highest provision of information, but the most cost-effective investigations were ultrasound and liver function tests. A software program produced a diagnostic accuracy of 84%.

The role of investigation is to determine whether or not a tumour is suitable for resection or palliation. The objective of palliation, which is the lot of the majority of patients, is to prolong life by relieving suffering, namely the obstructive jaundice and the luminal obstruction. Non-operative approaches are the preferred method. Evidence is not available to suggest that palliative resection has any advantage over non-operative palliation. Surgical palliation is reserved for the patient who is considered operable but at surgery found not to be so. Thus the surgical view of pancreatic cancer is that of operating on a suitable patient.

## Indications for resection

The ideal tumour is one which is locally confined and has a good prognosis. The histology is important, but this can usually be surmised from investigations. The rare benign and good prognostic non-duct cell carcinomas have characteristic radiological features and are more prevalent in the body and tail of the pancreas than in the head of the gland. Ampullary tumours are diagnosed endoscopically but their extent needs to be assessed radiologically. Biopsy, which is usually achieved by percutaneous techniques, is limited to the patient who is considered inoperable, however, rarely, as in neuroendocrine tumours, a biopsy is required if the tumour is submitted for pre-operative chemoradiotherapy. Indeed, it is recommended that before starting either chemotherapy or radiotherapy, a biopsy should be performed.

## Operability

For the patient suitable for resection the surgeon needs to know that the disease is confined to the pancreas and that a standard resection will encompass the tumour. The standard resection is a pancreatoduodenectomy which excises the duodenum, the head of the pancreas and the lower bile duct. Extended procedures which involve radical lymphadenectomy have not improved survival. Incomplete excisions do not improve survival; it behoves the surgeon to select the patient for resection in which the tumour is completely excised both macroscopically and microscopically.

The markers of inoperability are distant metastases, involved lymph nodes away from the pancreas and involvement of the portal vein or superior mesenteric artery. State-of-the-art helical CT scanning, with or without magnetic resonance imaging (MRI) should accurately predict operability in 60–70% of patients.

Laparoscopic examination of the abdominal cavity will, at most, improve this yield by 10%. The effect of endoscopic ultrasound, peritoneal washings, bone marrow biopsy and PET scanning have yet to be fully evaluated. It is cost-effective to limit the investigations to state-of-the-art CT scanning and accept a slightly higher rate of inoperable cases which can be managed by surgical palliation.

With selection the surgical outcome should be a mortality of under 5% and a 5-year survival of 20% for duct cell carcinomas. The quality of life for patients undergoing pancreatoduodenectomy is good and their initial recovery period is no longer than 3 months before achieving an acceptable normalization of life. Adjuvant chemotherapy improves survival by 10%. Radiotherapy does not improve survival and it may even be harmful.

### Conclusion

The surgeons' view of pancreatic carcinoma is that the diagnosis should be made early, the investigations should be undertaken expeditiously and the investigations limited to helical CT scanning. For those patients with an inoperable tumour a biopsy is appropriate. Operative mortality should be low and the quality of life following recovery from resection good.

### Key points

- (1) Incidence of disease far more common in the elderly
- (2) Histological type of great importance prognostically
- (3) Early diagnosis essential
- (4) Operability determined by high quality imaging
- (5) Resection associated with a <5% mortality and a 20% 5-year survival

### Further reading

- [1] Kloppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. Histological typing of tumours of the exocrine pancreas. International Histological Classification of Tumours, 2nd Edition. Berlin: Springer. World Health Organisation, 1998: 1–61.
- [2] Lillemoe KD, Cameron JL, Yeo CJ, Sohn TA, Nakeeb A, Sauter PK, Hruban RH, Abrams RA, Pitt HA. Pancreaticoduodenectomy. Does it have a role in the palliation of pancreatic cancer? *Ann Surg* 1996; 223: 718–25.
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- [4] Yeo CJ, Cameron JL, Sohn TA, Coleman J, Sauter PK, Hruban RH, Pitt HA, Lillemoe KD. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. *Ann Surg* 1999; 229: 613–22.

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## Carcinoma of the pancreas: detection and staging using CT and MRI

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Our ability to diagnose pancreatic carcinoma has improved substantially over the past 20 years, owing to major advances in pancreatic imaging, including the development of US, CT and MRI. Despite these advances, however, the prognosis of patients with pancreatic cancer remains dismal. The overall 5-year survival rate is only 3%<sup>[1]</sup>, although the 5-year survival rate for patients who undergo pancreatic resection is reported to be approximately 20%<sup>[2–4]</sup>. Because of the very poor prognosis of patients with pancreatic carcinoma, many physicians take a nihilistic approach to its diagnosis and staging. It is important to keep in mind, however, that a large percentage of patients with pancreatic cancer who undergo laparotomy for possible curative resection are found to have unresectable disease. Thus, optimization of pre-operative imaging is important in order to

reduce the percentage of patients who are unnecessarily subjected to laparotomy.

CT has become established as the primary initial imaging method for both detection and staging of suspected pancreatic carcinoma. Most studies have found that CT is highly reliable when it demonstrates features indicating that a tumor is unresectable<sup>[5,6]</sup>. The positive predictive value (PPV) of a diagnosis of unresectability with helical CT has ranged from 92% to 100%<sup>[7–11]</sup>. Helical CT is less reliable, however, for predicting that a tumor is resectable (PPV=76–90%)<sup>[7–11]</sup>. Nevertheless, this represents a substantial improvement over prediction of resectability with conventional CT (PPV=45–72%)<sup>[12–14]</sup>. Limitations of CT include: poor ability to demonstrate small hepatic or peritoneal metastases; inability to demonstrate microscopic