Pancreatic Cancer

Progress in the treatment of a deadly disease

by Dr Cheah Yee Lee

Pancreatic cancer (adenocarcinoma) is a lethal disease with poor prognosis. The average lifetime risk of developing pancreatic carcinoma is one in 67 (1.5%) with an increasing number of cases diagnosed each year. The average five-year survival rate for pancreatic cancer is only 5%. Death rates from pancreatic cancer have continued to increase in Europe since 2000.[1]

Surgical resection of pancreatic cancer remains the only chance for cure. In the last 20 years, continued progress has been made in the development of more effective perioperative management and refinement of surgical techniques. This article will discuss the current management of pancreatic cancer.

Why is Pancreatic Cancer Such a Deadly Disease?

The poor prognosis of pancreatic cancer is due to several factors. Early stage pancreatic cancer (when it is most treatable) commonly remains asymptomatic. A small pancreatic tumour at the head of the pancreas may cause painless jaundice due to obstruction of the common bile duct, but cancer at other locations in the pancreas routinely does not cause symptoms until the tumour has become locally advanced or metastatic. Up to 80% of patients with pancreatic cancer will present at a late stage of the disease. Their symptoms may include pain (back pain caused by invasion of celiac nerve plexus), jaundice, weight loss, poor appetite and steatorrhoea.

There is no effective screening method for detecting early pancreatic cancer at the asymptomatic stage in the general population. Carbohydrate Antigen 19-9 (CA 19-9) is a commonly used tumour marker for pancreatic cancer with sensitivity and specificity rates of 79% and 82% respectively. The main disadvantage of using CA 19-9 for screening is its high false positive rate; it is commonly elevated in other hepatobiliary conditions e.g. jaundice due to non-cancerous aetiologies, hepatitis, cirrhosis and chronic pancreatitis. Therefore, CA 19-9 is not recommended for screening of pancreatic cancer in the asymptomatic general population by the American Society of Clinical Oncology as its positive predictive value is low (0.5-0.9%).[2]

The tumour biology of pancreatic cancer is such that it is one of the most intrinsically drug-resistant tumours. In advanced unresectable cases, chemotherapy alone offers a limited survival advantage of a few months (median survival five to nine months). There is also a high rate of relapse, even among early stage patients who underwent surgical resection and adjuvant chemotherapy.

Risk Factors for Pancreatic Cancer

Smokers are twice as likely to develop pancreatic cancer compared to non-smokers. Obese people are at a 20% increased risk of pancreatic cancer. Other risk factors include age and family history. In some families, their risk of pancreatic cancer is due to inherited gene mutation syndromes e.g. mutation in BRCA2 (hereditary breast and ovarian cancer syndrome).

The Best Radiological Modalities to Investigate Pancreatic Cancer

The first line of imaging for patients with suspected pancreatic cancer is a multidetector computed tomography (CT) scanning of the abdomen. This is usually performed with oral water contrast and intravenous iodinated contrast, scanning with thin (2mm-3mm) collimation during the pancreas phase. Pancreatic adenocarcinoma usually appears hypodense (darker) or isodense (similar brightness) compared to the rest of the pancreas **[Figure 1].** Characteristics of the lesion on CT can usually distinguish

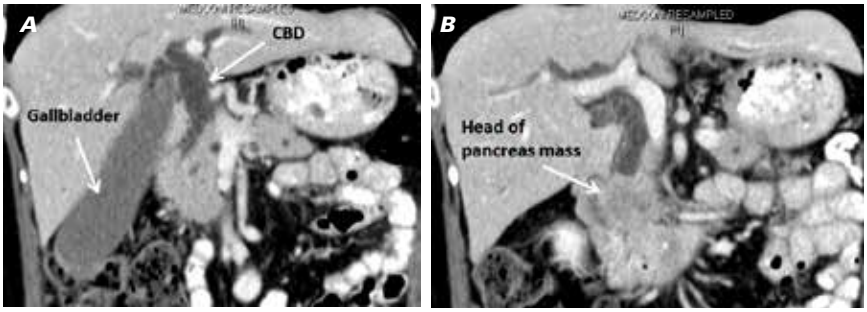

Figure 1. ***Multidetector CT Abdomen in a 65-year old lady who presented with obstructive jaundice***
A. enlarged gallbladder and dilated CBD.
B. head of pancreas mass causing obstruction of distal CBD.

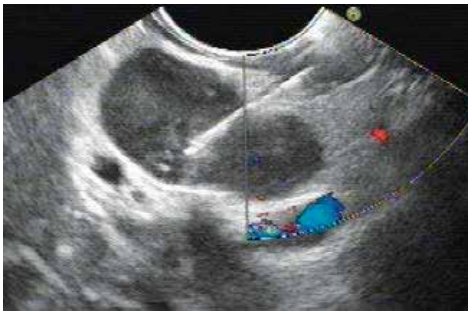

Figure 2. ***EUS-FNA: ultrasound images via EUS guided FNA (seen as white needle tract) of a mass in the pancreas.***

adenocarcinoma from other types of pancreatic masses e.g. cystic pancreatic neoplasms and neuroendocrine tumours.

Another option for cross-sectional scanning is magnetic resonance imaging (MRI) of the abdomen. MRI uses magnetic waves and therefore does not expose the patient to radiation. It is, however, more expensive, takes longer to complete and may be limited by artefacts. CT and MRI have similar results in the detection and assessment of resectability for pancreatic carcinoma.

After detection of the pancreatic mass, further imaging of other parts of the body may be required to rule out metastatic disease and to stage the disease.

Obtaining a Tissue Biopsy for Diagnosis

After appropriate imaging studies and staging, patients with resectable pancreatic cancer who are fit for major surgery do NOT necessarily need a histological confirmation of the diagnosis prior to surgery. A biopsy should be performed if other diagnoses which mimic pancreatic adenocarcinoma are suspected, particularly in chronic or autoimmune pancreatitis (young age, history of autoimmune disorders, alcohol abuse and equivocal findings on imaging).

Endoscopic ultrasound (EUS) – guided biopsy is the best method for obtaining a tissue diagnosis **[Figure 2].** An endoscopic ultrasound is a specialised side-viewing endoscope which is combined with an ultrasound probe at the tip of the scope. It is advanced into the stomach and duodenum (like an oesophagogastroduodenoscope) and used to visualise adjacent structures, particularly the pancreas and common bile duct. For diagnosis of solid pancreatic masses, EUS has a sensitivity of 78%-95% and a specificity of 75%-100%; it is more accurate than CT for small < 1cm pancreatic masses.

A fine-needle aspiration (FNA) biopsy of the pancreatic mass may be performed under direct ultrasound guidance using the EUS. EUS-FNA has a high positive predictive value (99%) and a negative predictive value of 64% (false negative ~35%-40%). Most surgeons will offer resection if imaging is suspicious for cancer even though FNA negative. EUS is also useful for evaluation of vascular invasion of adjacent portal vein, superior mesenteric vein, superior mesenteric artery and celiac axis.[3]

If EUS is not available, tissue diagnosis may be obtained using percutaneous FNA with image guidance.

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Table 1. ***Defining unresectable versus borderline resectable pancreatic cancer***

Unresectable	Borderline Resectable
Distant metastases	Severe unilateral or bilateral SMV or PV infringement
Direct involvement of the SMA, IVC, aorta, coeliac axis or hepatic artery	Less than 180 degree tumour abutment on the SMA or celiac
Extensive peripancreatic lymphatic involvement	Reconstructible abutment of the hepatic artery
	Reconstructible short segment SMV occlusion

SMV: superior mesenteric vein; PV: portal vein; SMA: superior mesenteric artery; IVC: inferior vena cava

Surgical Options for Resectable Pancreatic Cancer

For tumours in the head of the pancreas, the conventional pancreaticoduodenectomy (Whipple) procedure removes the pancreatic head, duodenum, proximal jejunum, gallbladder, common bile duct and partial gastrectomy. Modern modifications to this technique include the pylorus-preserving pancreaticoduodenectomy (PPPD), which preserves the gastric antrum and pylorus. This technique decreases the complications associated with a partial gastrectomy and has similar long-term survival compared to the Whipple procedure **[Figure 3].**[4]

For tumours in the body and tail of the pancreas, surgical resection usually involves a distal pancreatectomy and splenectomy. This may be performed laparoscopically though data assessing the oncological long-term outcome compared to the open technique is still limited.

Post-operative Outcomes for the Major Operations

Mortality risk from a pancreaticoduodenectomy is < 5% in subspecialised hepatopancreatobiliary units.[5] Complication rates range from 25%-30% including pancreatic leak, bile leak, delayed gastric emptying, intraabdominal infection, wound infection, diarrhoea, weight loss and diabetes (usually only in patients with abnormal blood sugars pre-operatively). The main concern in a distal pancreatectomy is pancreatic leak rate of 15%-20%.

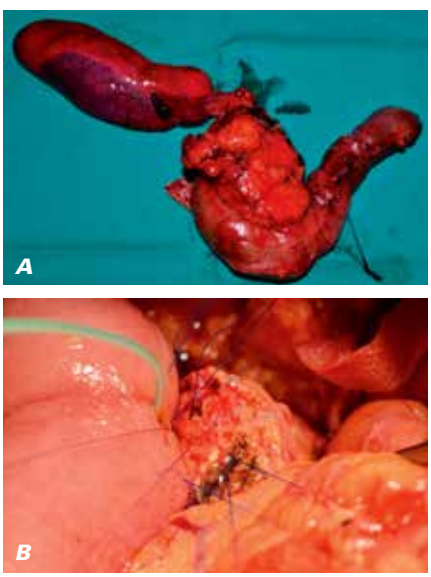

Figure 3. ***The previously mentioned 62-year old lady underwent a pylorus preserving pancreaticoduodenectomy (PPPD)***
A. operative specimen.
B. mucosa to mucosa pancreaticojejunostomy anastomosis.

Treatment of Focal SMV or PV Invasion

Pancreatic cancer in the head of the pancreas may invade the adjacent SMV or PV. In these situations, a pancreaticoduodenectomy with vein resection and reconstruction is the standard approach, provided that adequate inflow and outflow veins are present and an R0/R1 resection can be accomplished. The SMV and PV may be reconstructed using primary anastomosis or using an intervening vascular graft.

Necessity of Adjuvant Treatment after Surgical Resection of Pancreatic Cancer

Chemotherapy with or without radiotherapy is usually recommended after resection of pancreatic cancer. Most chemotherapy regimens are gemcitabine-based.

The Role of Neoadjuvant Treatment

Patients with non-metastatic unresectable or borderline resectable disease may be referred for neoadjuvant therapy prior to surgical exploration in an effort to downstage to resectability. This is usually provided in the context of a clinical trial. There is limited evidence on the outcomes of specific neoadjuvant therapy protocols. Some centres have reported induction of resectability in 30%-40% of patients after neoadjuvant treatment. Once resected, overall survival is comparable to similarly staged patients who were primarily resected.

Conclusion

Pancreatic adenocarcinoma is a lethal cancer due to poor biology and late presentation. Surgical resection remains the best chance for cure and outcomes of resection have steadily improved due to refinement of techniques and perioperative management. In borderline resectable pancreatic cancer, neoadjuvant chemotherapy may induce resectability. MG

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