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# Pancreatic cancer

## Current management

### BACKGROUND

Pancreatic cancer remains a common and lethal cancer with a median survival of approximately 6 months.

### OBJECTIVE

This article discusses the current management of pancreatic cancer, both potentially curative and palliative treatment.

### DISCUSSION

Surgical resection of the primary tumour is only possible in about 10% of cases as many patients have locally advanced or metastatic disease at the time of presentation. For the majority of patients, treatment is palliative and may include surgical treatments or endoscopic or percutaneous stenting to relieve obstructive jaundice or gastric obstruction, chemotherapy, radiotherapy or interventional radiological techniques. Adequate pain relief and treatment of pancreatic insufficiency are important components of treatment.

**Pancreatic cancer is the fifth commonest cause of** cancer related deaths in Australia.<sup>1</sup> Very little progress has been made in understanding the aetiology of this disease. The majority of patients have distant metastases or advanced local disease at the time of presentation and are unable to undergo surgical resection. Therefore for the majority of patients, the aim is to palliate symptoms and to maintain quality of life.

### Diagnosis and assessment

The mainstay of diagnosis remains abdominal ultrasound (*Figure 1*) and computerised tomography (CT) scanning in the investigation of patients presenting with obstructive jaundice. However, there is great variation in the quality of abdominal CT scanning with the best images and assessment being obtained with a pancreatic protocol abdominal CT.

Metastatic disease is most commonly seen in the peritoneum and liver and in these patients surgical resection is of no benefit. The commonest reason for a tumour being unresectable is local invasion of nearby major vessels (superior mesenteric vein, portal vein, hepatic artery or superior mesenteric artery). This is termed 'advanced local disease'. For tumours that appear resectable after CT scanning, many units will perform

further staging with either endoscopic or laparoscopic ultrasound examination<sup>2</sup> (*Figure 2*). More accurate initial staging has led to less patients undergoing failed attempts at resection.

### Management

#### Pancreatic resection

About 10% of patients will be considered for surgical resection and this remains the only potentially curative treatment for pancreatic cancer. Even in this highly selected group of patients, 5 year survival rates of 10–25% are reported.<sup>3–5</sup> Patients with ampullary, duodenal and neuroendocrine tumours have a greater chance of cure following resection but only account for about 20% of tumours involving the head of the pancreas.

The value of preoperative biliary drainage with endoscopic stenting before consideration of resection continues to be debated.<sup>6,7</sup> Due to the presence of sepsis or the impact of hospital waiting lists, the majority of patients will ultimately undergo endoscopic biliary drainage before or during staging of their pancreatic tumour.

A Whipple resection (pancreaticoduodenectomy) involves resection of the gallbladder, bile duct, duodenum, pancreatic head and uncinate process as

well as varying amounts of peripancreatic lymph nodes and the stomach. It remains a major operation with an accepted operative mortality of around 5% and morbidity of 40%; however this is significantly better than 20 years ago. The commonest complication remains delayed gastric emptying while the most dangerous is leakage of pancreatic fluid with associated necrosis, infection and haemorrhage. Variations of the reconstruction after resection are numerous with none as yet demonstrating a significant advantage over others.

The mortality of pancreatic resection has been found to be proportional to both the number of pancreatic resections performed by an individual surgeon as well as the institutional load of major surgical cases.<sup>8,9</sup> Referral to a surgical centre with a high volume of pancreatic surgery is strongly recommended.

Extended lymphadenectomy has recently been examined in a randomised control trial against standard lymphadenectomy with no survival advantage.<sup>10</sup> Complications from extended resection were high, probably related to dysfunction of the gut secondary to the division of the enteric nerve supply around the superior mesenteric artery.

### Adjuvant therapy

Neo-adjuvant chemo-radiotherapy has been advocated in the treatment of pancreatic cancer, although there is little evidence as yet to support this. For patients with advanced local disease, downstaging with chemo-radiotherapy is rarely successful.<sup>11</sup>

Following pancreatic resection, adjuvant chemotherapy has become standard for pancreatic adenocarcinoma. This is based on results of the European Study Group for Pancreatic Cancer (ESPAC) – 1 trial that compared adjuvant chemotherapy (5-fluoruracil [5FU]), adjuvant chemo-radiotherapy and no further treatment following pancreatic resection.<sup>12</sup> There was a survival benefit for adjuvant chemotherapy (median survival 19.7 months vs. 14.0 months [ $p=0.0005$ ]). There is no proven role for adjuvant radiation therapy. Currently ESPAC – 3 is recruiting patients in Australia and comparing 5FU with gemcitabine.

### Palliative management of advanced local or metastatic disease

Treatment depends upon the probable length of survival, presence of metastatic disease or advanced local disease as well as symptoms. Common symptoms include jaundice, weight loss, pain, and vomiting from gastric outlet obstruction (*Figure 3*). Median survival for all patients is only 6 months, however for patients

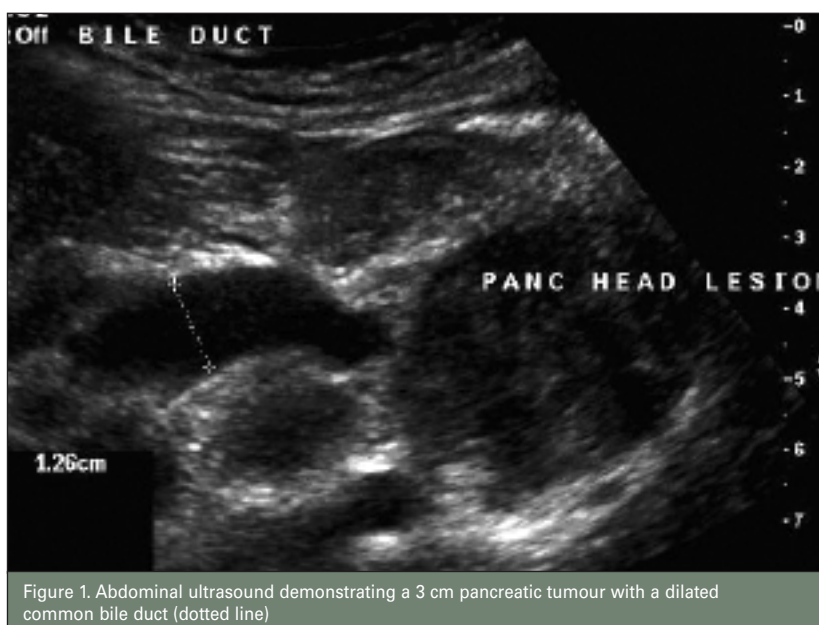


Figure 1. Abdominal ultrasound demonstrating a 3 cm pancreatic tumour with a dilated common bile duct (dotted line)

with advanced local disease without metastatic disease median survival is around 11 months.

Palliation of pancreatic cancer may involve:

- endoscopic stenting
- surgery
- chemotherapy
- radiotherapy, and/or
- interventional radiologic techniques.

### Obstructive jaundice

Median survival is similar following endoscopic stenting or surgical bypass.<sup>13</sup> In a meta-analysis of three trials comparing surgery to the use of plastic biliary stents there was no difference in 30 day mortality, however more treatment sessions were required for patients treated nonoperatively (OR: 7.23, CI: 3.73–13.98).<sup>14</sup> In the majority of patients, the decision will depend on: the patient's age, medical fitness, tumour type, and level of c-reactive protein, the presence of liver metastases, and the preference of the treating institution.<sup>15</sup>

### Nonsurgical techniques

Relief of jaundice by endoscopic drainage is effective in approximately 80% of cases,<sup>16</sup> although success rates of up to 97% have been reported.<sup>17</sup> Perforation and pancreatitis are unusual complications and antibiotic coverage of biliary flora is required to prevent cholangitis. In patients in whom endoscopic drainage is not possible, percutaneous stenting is usually effective in resolving jaundice. Pancreatitis, haemorrhage and biliary peritonitis have all been described as complications of percutaneous stent placement. Expandable metal stents placed by an

endoscopic<sup>18</sup> or percutaneous route<sup>19</sup> have also been successfully used in the palliation of pancreatic cancer with low morbidity and mortality rates.

### Surgical techniques

In patients who undergo a trial dissection and are found to be unresectable, palliative biliary bypass as well as gastroenterostomy are usually performed to palliate jaundice and possible later gastric outlet obstruction. Many surgeons still consider biliary bypass to be the best palliative management in fit patients. In experienced centres, operative bypass for palliation of pancreatic

cancer can be performed with hospital mortality as low as 0–2%<sup>22,23</sup> and morbidity rates of around 35%.<sup>23</sup> Laparoscopic biliary and gastric bypass has been described<sup>24</sup> with low morbidity rates (7–25%).<sup>24–26</sup>

### Gastric outlet obstruction

The true incidence and natural history of gastric outlet obstruction in patients with pancreatic cancer is unclear. A proportion of patients with vomiting will have a delayed gastric emptying secondary to neural invasion or as a paraneoplastic phenomenon.<sup>27</sup> Gastric bypass will not benefit these patients and prokinetic agents such as metoclopramide and erythromycin may be beneficial.

In patients with potentially resectable disease, the best option is resection if possible, and operative bypass if the tumour is found to be unresectable at laparotomy. For patients with unresectable disease on CT staging, consideration should be given to laparoscopic gastroenterostomy with endoscopic biliary stenting, or duodenal stenting. In a patient with unresectable pancreatic cancer and gastric outlet obstruction, survival may be as little as 4 weeks.

Endoscopic duodenal stenting has been shown to be a safe technique, significantly improving quality of life and dysphagia scores.<sup>28</sup> Recurrence of symptoms may occur in approximately 25% of patients but this can often be managed by repeat endoscopic techniques.<sup>29</sup> Several small comparative series have shown a shorter hospital stay and earlier oral intake following duodenal stenting in comparison to operative gastroenterostomy.

Laparoscopic gastroenterostomy is technically easier to perform than laparoscopic biliary bypass. Most series are small, however patients have a shorter hospital stay than those who are treated with open surgery<sup>30</sup> with resolution of gastric outlet obstruction in most patients.<sup>31</sup>

### Tumour directed therapy

Chemo-radiotherapy is frequently used in the palliation of patients with advanced local disease. 5-fluoruracil or gemcitabine can be used as a radio sensitising agent; survival has been shown to be approximately doubled in comparison to no treatment. For patients with metastatic disease, the mainstay of treatment is palliative chemotherapy. While significant symptom control and quality of life improvements have been demonstrated, the impact on survival is limited.

### Pain management

Quality of life can be seriously impaired by pain due to pancreatic carcinoma, and often this is the symptom most feared by patients. The presence of pain has been

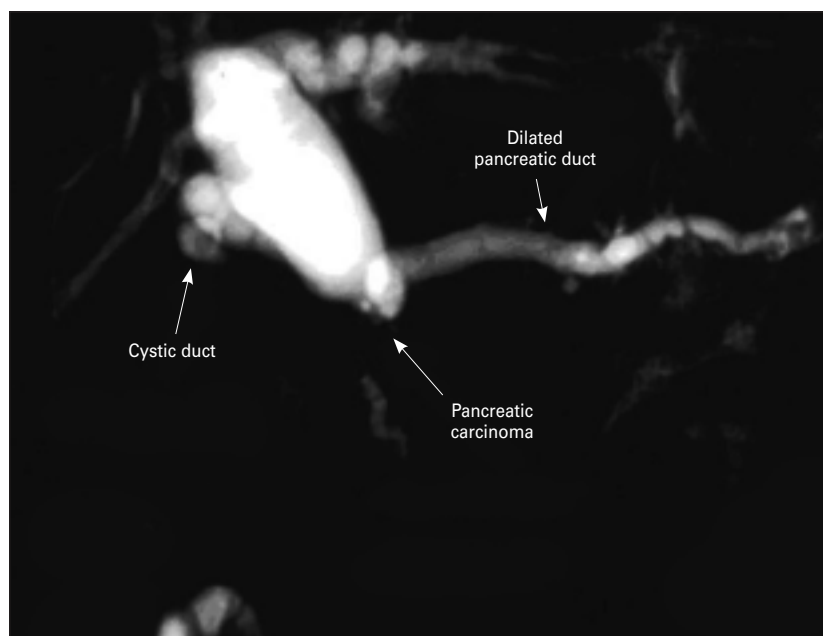


Figure 2. Magnetic resonance cholangiopancreatography (MRCP) demonstrating pancreatic cancer. The pancreatic carcinoma is not seen but the arrow shows a stricture in the common bile duct

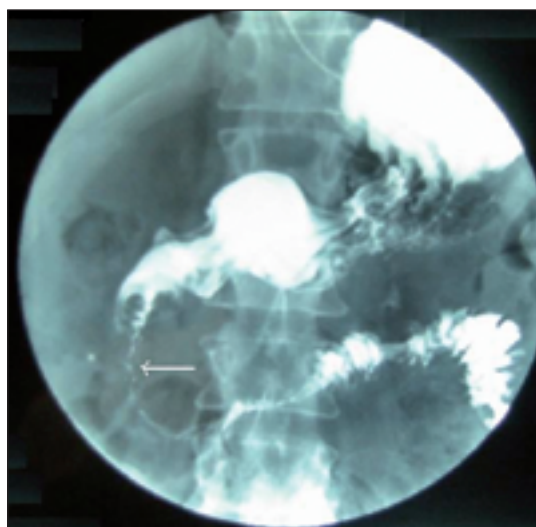


Figure 3. Barium meal demonstrating gastric outlet obstruction. It shows obstruction of the second part of the duodenum due to extrinsic pressure from pancreatic cancer

shown to have strong correlation with survival.<sup>32</sup> Every patient presents as a distinct scenario and therefore pain management needs to be individualised. Many patients may be managed with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination with the many opiate preparations. Pain management can usually be performed on an outpatient basis and monitored by the general practitioner with or without involvement of a palliative care service.

Combination therapy with chemotherapy and radiotherapy improves pain control in around 39% of patients treated with gemcitabine, with lower rates for 5FU.<sup>33</sup> Radiotherapy alone can also provide pain relief.<sup>34</sup>

Pain fibres from the pancreas synapse in the coeliac ganglion and then run within the major and minor splanchnic nerves to the spinal column. Pain relief can be obtained by disruption of this pathway within the abdomen or thorax. Radiological and surgical techniques for coeliac plexus neurolysis have had variable success rates.<sup>35–38</sup> More recently coeliac plexus blockade has also been performed with minimal morbidity using endoscopic ultrasonographic (EUS) guidance.<sup>39</sup>

Division of the splanchnic nerves within the thorax can also disrupt the pancreatic pain neural pathway. Originally described by open thoracotomy, several authors have described the use of video assisted thoracoscopy to divide the sympathetic nerves within the chest, palliating resistant pancreatic cancer pain.<sup>31,40,41</sup>

### Pancreatic insufficiency

Obstruction of the pancreatic duct may lead to symptoms of pancreatic insufficiency such as steatorrhoea and weight loss. Often overlooked as a symptom, the addition of oral pancreatic exocrine supplements will usually control these symptoms. Pancreatic endocrine insufficiency (diabetes mellitus) should be treated as type 2 diabetes.

### The future

Future novel techniques may provide improved palliation than we can currently provide. Most promising are novel biological agents that target the epidermal growth factor receptor or angiogenesis.<sup>42</sup> Electrolytic ablation of pancreatic lesions may be possible.<sup>43</sup> Palliation of symptoms may include endoscopic pancreatic duct drainage. Early results with gemcitabine combined with xeloda (an oral form of 5FU) demonstrating improvements over the result seen with gemcitabine alone suggest this may become the new standard. Newer radiation techniques will permit more precise

tumour targeting. Better imaging with CT scanning, magnetic resonance imaging (MRI), laparoscopy, and laparoscopic ultrasound will also help in the selection of patients for palliative techniques.

Overall pancreatic cancer remains a lethal disease and in the near future improvements in care are likely to be based around palliation rather than improvements in curative treatment.

Conflict of interest: none declared.

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