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Improving outcomes in pancreatic cancer

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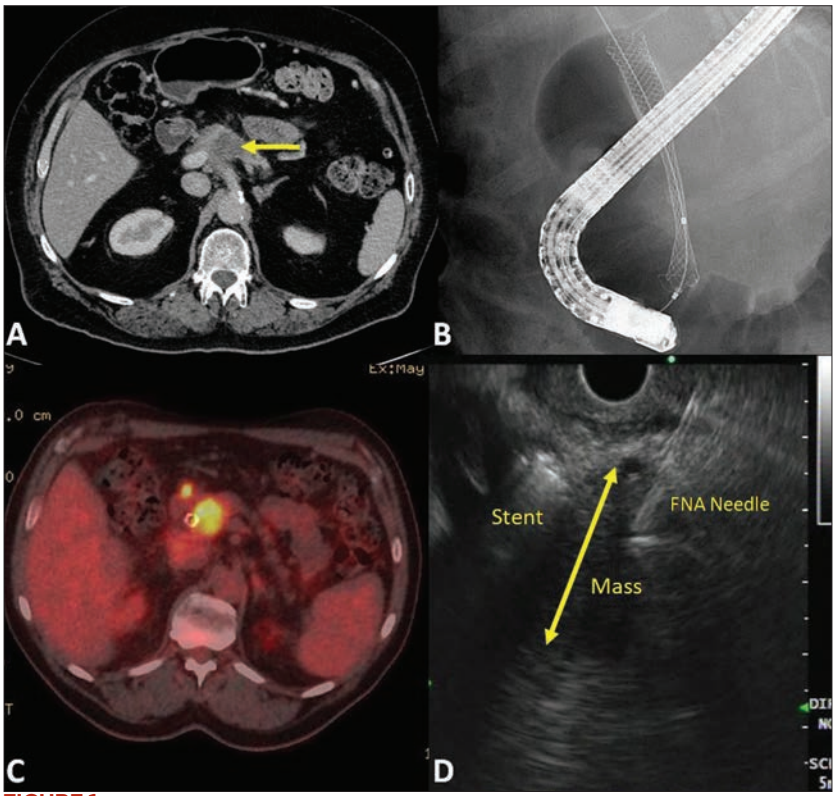

FIGURE 1
Pancreatic cancer assessment: (A) Diagnostic CT scan showing inoperable mass in body of pancreas invading the coeliac artery and plexus (arrow) causing epigastric pain. Position of tumour behind air in stomach prevents visualisation with trans-abdominal ultrasound. (B) Compression of tumour onto bile duct requires insertion of a metal bile duct stent to relieve jaundice at endoscopy. (C) Positron emission tomography scan is indicated to obtain further staging information in cancers that are operable. A stent has been placed adjacent to the tumour and further hot spot seen above but no liver disease seen. (D) A difficult tumour position often requires an endoscopy with ultrasound (EUS) to take a fine needle aspiration sample with the endoscope in a similar position to picture (B). Palliative coeliac plexus nerve blocks can also be placed during an EUS procedure

How do patients with pancreatic cancer present?

How should diagnosis be confirmed?

What are the treatment options?

PANCREATIC DUCTAL ADENOCARCINOMA HAS A VERY POOR PROGNOSIS. THE CURRENT FIVE-YEAR survival rate for pancreatic cancer is 3% in the UK. There were 9,921 patients diagnosed with pancreatic cancer in the UK in 2015 and almost an equal number of patients (9,263) dying from the disease in 2016.[1]

There has been little improvement in outcomes for this disease in the past 40 years.[2] Pancreatic cancer is the eleventh most common cancer in the UK. However, its poor outcomes make it the fifth most common cause of cancer deaths.[1] The incidence of pancreatic cancer is increasing by 2% per year and when coupled with its poor outcomes and treatment for other cancers becoming more effective means that pancreatic cancer is likely to supersede breast cancer as at least the fourth most common cause of cancer deaths in the UK by 2035.[3]

Relative survival rates for pancreatic cancer in the UK are lower than the average for Europe.[2]

The combination of an aggressive disease, vague presenting symptoms and poor sensitivity of standard diagnostic tests is a key factor contributing to poor outcomes with only 15% of patients with pancreatic cancer having operable disease at diagnosis. This article focuses on the recognition of symptoms and risk factors that can aid early referral, diagnosis and treatment to improve outcomes for a disease that has such a relatively short survival compared with other cancers that it has been referred to as a medical emergency.[4]

In February 2018, NICE published a clinical guideline on pancreatic cancer in adults (NG85) to help improve early detection and management.[5]

PRESENTATION

Diagnosis at an early stage is associated with improved survival therefore it is important to note the high-risk symptoms that require investigation. Patients may present with symptoms »

Table 1

NICE referral recommendations for suspected pancreatic cancer symptoms (NG12)[53]

- Suspected cancer pathway referral if 40 and over with jaundice
- Consider urgent direct access CT scan (or an urgent ultrasound scan if CT is not available)* in people aged 60 and over with weight loss and any of the following:
  - Diarrhoea
  - Back pain
  - Abdominal pain
  - Nausea
  - Vomiting
  - Constipation
  - New onset diabetes

* see Confirming diagnosis section (column 2 below) re limitations of ultrasound

Table 2

Presentations of pancreatic cancer (Adapted from Pancreatic Cancer Action. Pancreatic cancer symptoms & signs)[54]

- New-onset irritable bowel in patients over the age of 40 years
- Patients aged over 40 years, who present with weight loss, abdominal pain, and alteration in bowel habit, who have not attended the surgery for a considerable time
- New-onset diabetes not associated with weight gain
- New-onset and persistent dyspepsia (unresponsive to proton pump inhibitors)
- Persistent epigastric or back pain
- The rare attender who suddenly appears at the surgery, often makes multiple visits, with unexplained weight loss, epigastric pain, and alteration in bowel habit

of local compression or invasion of mesenteric nerves or the bile duct (see figure 1, p11), changes in bowel habit caused by alterations in exocrine pancreatic function and new onset diabetes. There have been a number of studies looking at symptom presentation of pancreatic cancer and the increased risk associated with each one.[6]

The recommendations for urgent referral for suspected pancreatic cancer listed in the NICE guideline *NG12. Suspected cancer: recognition and referral*, are shown in table 1, above.

Jaundice, with or without pain, has been shown to have a positive predictive value (PPV) of 22% in patients aged ≥ 60 and although other symptoms listed have been shown to have a PPV of < 1% as a single symptom, when combined with weight loss in patients over 60 this increases to 1.5-2.7%.[7]

Although pancreatic cancer has a peak incidence in patients in their ninth decade,[8] 37% of patients present under the age of 70 and 14% are under 60, therefore some cancer charities promote consideration of urgent referral or investigation in all patients over 40 with unexplained symptoms not just those who are jaundiced (see table 2, above). This practice is more in keeping with a GP's gut feeling which has been shown to be a strong predictor of pancreatic cancer in one Danish study (PPV = 22.5%) highlighting the need for direct access computerised tomography (CT).[9]

A rarer neuroendocrine type of pancreatic tumour exists which can have a more benign course. Neuroendocrine tumours account for only 1.5% of all pancreatic cancers and are often found incidentally or secrete certain hormones. Their complex management is outside the scope of this article which refers to pancreatic cancer as the ductal adenocarcinoma type.[10]

EXAMINATION AND ASSESSMENT

It has been shown that nearly a third (31.4%) of patients present to their GP at least three times before a diagnostic test is carried out or a referral is made.[10] A full-time GP would only be expected to see one case of pancreatic cancer in five years,[7] therefore it is important to note the high-risk symptoms that necessitate investigation and referral. Unfortunately, current urgent cancer referral pathways have a poor sensitivity and only detect 15% of pancreatic cancers. A significant number of patients with pancreatic cancer present with worsening symptoms of vomiting from duodenal compression or jaundice which results in 50% of patients being diagnosed via an accident and emergency presentation.[11,12]

Given the position of the pancreas (see figure 1, p11), it is difficult to detect a pancreatic mass on examination. A detailed history of any weight loss (rather than BMI), developing chronic abdominal pains, obstructive projectile vomiting or persistent nausea and clinical detection of jaundice requires urgent investigation and exclusion of differential diagnoses, see table 3, above.

CONFIRMING DIAGNOSIS

Pancreatic cancer requires a CT scan for diagnosis (see figure 1, p11). There are a number of symptoms in patients when either direct access CT scan is suggested or urgent referral if not available.

Trans-abdominal ultrasound is excellent at detecting gallstones and bile duct dilatation to confirm obstructive jaundice, however the presence of gas in the stomach makes visualisation of the pancreas poor. NICE recommends an urgent ultrasound scan if CT is not available, see table 1, above.* However, although pancreatic abnormalities can be detected on ultrasound, especially in thin people, if the ultrasound scan is negative this should not deter urgent referral.

Table 3

Differential diagnosis of pancreatic cancer[55]

- Chronic pancreatitis
- Bile duct stones
- Ampullary carcinoma
- Cholangiocarcinoma
- Autoimmune pancreatitis
- Gastric cancer
- Peptic ulcer disease
- Functional dyspepsia

The differential diagnosis of symptoms can also meet the criteria for an urgent gastroscopy to exclude an upper gastrointestinal tumour or lesion and it is important to consider a CT and follow-up for patients with epigastric 'dyspepsia' that have either a normal gastroscopy or symptoms that have not responded to anti-acid therapy, see table 2, above.

Liver function blood tests should be performed to exclude or confirm jaundice. The serum tumour marker CA19-9 is not recommended for initial diagnostic assessment as levels can be significantly raised in obstructive jaundice from benign disease.[13]

CT has a high accuracy for staging and planning surgical resection.[14] However, if the diagnosis is unclear or the tumour is not resectable then tissue sampling is required. This enables exclusion of atypical tumours to plan appropriate palliative chemotherapy.

Because of its location pancreatic tissue sampling is usually performed using endoscopic ultrasound (EUS) with fine needle aspiration (FNA). By passing an endoscope with a small ultrasound probe attached into the stomach and duodenum, the EUS probe is able to lie directly against the pancreas and sample abnormal areas.

Although the procedure has a low risk of complications (2.7%)[15] the wider scope and the lengthy duration of the procedure requires the patient to be sedated.[16] If liver metastases are present then a liver biopsy is an alternative option.

RISK FACTORS

Modifiable pancreatic cancer risk factors include obesity and smoking. However, two-thirds of pancreatic cancer tumours are attributable to the random mutations that occur throughout an individual's lifetime. There is an increased incidence of pancreatic cancer in a number of conditions including chronic pancreatitis (three fold) and hereditary pancreatitis (50 fold).[1,5] Surveillance for pancreatic cancer is currently recommended in hereditary pancreatitis, Peutz-Jeghers syndrome and patients with high-risk gene mutations who have a first-degree relative with pancreatic cancer.[6] Annual MRI can be performed to look for early cancers, but given a lack of further evidence regarding the ideal timing of initiation or interval for screening it should be discussed and led by a secondary care specialist unit.[5,17,18]

Pancreatic cysts have been shown to account for a small proportion < 5% of pancreatic cancers. Although most cysts are benign or inflammatory, those containing mucin have malignant potential (termed either a mucinous cyst adenoma or intraductal papillary mucinous neoplasm).

The risk of a mucinous cyst becoming malignant is small (estimated at 0.72% per year).[19] However if these cysts are removed before malignancy is detected outcomes are improved. Overall five-year survival after resection is 87% for all cystic lesions and 62% for those with malignancy.[20]

Pancreatic cysts are found incidentally on 2.6% of CT scans and given the increased uptake of cross-sectional imaging pancreatic cysts are becoming increasingly identified and potentially a cause of significant anxiety.[21]

Patients with a pancreatic cyst should be referred to secondary care for characterisation so that a decision can be made regarding further management, based on identified risk factors such as pancreatic duct enlargement.[22,23]

MANAGEMENT

Staging

Management options are discussed at a specialist pancreatic cancer multidisciplinary team (MDT) meeting involving specialist consultant surgeons, radiologists, pathologists, oncologists, gastroenterologists, palliative care physicians and also crucially attended by cancer nurse specialists and specialist dietitians. Investigation results are coupled with the patient's fitness for surgery, chemotherapy and palliative options with the final decision made together with the patient after the clinician carefully explains the recommended treatment options.

Tumours are staged with a CT which is 80% accurate[14] and additional information then gained from either a positron emission tomography (PET)-CT scan, MRI of the liver or an EUS and FNA if required (see figure 1, p11) to enable tumour node metastasis (TNM) staging, see table 4, below. Clinically the TNM stage classifies patients into those with pancreatic cancer that are surgically resectable, locally advanced or metastatic. Only 15% of pancreatic cancers present at a resectable stage[24] so management is predominantly palliative.

Curative surgery

Comorbidity plays a significant role when considering a surgical option as well as tumour size and proximity to vessels. Tumours in the head of the pancreas are removed with a Whipple's procedure, for those in the body and tail a distal pancreatectomy is generally performed which usually removes the spleen as well. Pancreatic surgery is a significant undertaking as although the hospital mortality rates following surgery are below 2%, overall morbidity is up to 60%.[25] As with most cancer centres, surgical outcomes for pancreatic cancer correlate with both numbers of cancers seen and operations performed with significantly lower mortality and morbidity at high volume centres. With the establishment of specialised cancer centres in the UK, the two-year survival among resected patients has increased by more than 10%.[26] This association also applies to long-term survival and is multifactorial.[27,28]

Adjuvant chemotherapy is recommended after pancreatic cancer resection based on several randomised controlled trials which have shown that postoperative five year survival is increased from 8% to 21-23%.[29,30]

No definite advantage has been shown to recommend neoadjuvant therapy so therefore it is currently only considered for patients with resectable or borderline resectable pancreatic cancer in clinical trials.[5]

Palliative chemotherapy

First-line therapy for non-resectable pancreatic cancer in patients with a good performance status is usually gemcitabine increasing 12-month survival from 2 to 18%, however a significant response is seen in only 28% of patients [31] therefore a combination regimen is recommend if patients are well enough to tolerate this.[32]

For metastatic pancreatic cancer a combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) has been shown to prolong survival from 6.8 months with gemcitabine alone to 11.1 months. However, this treatment does have significantly more adverse effects and therefore should only be considered in patients with a very good performance status.[33] Lastly, albumin-bound paclitaxel (nab-paclitaxel) in combination with gemcitabine has been shown to give some benefit, mean survival 8.5 versus 6.7 months without.[34]

Biliary and duodenal obstruction

Jaundice is present in up to 70% of patients with pancreatic cancer. Jaundice causes lethargy, anorexia and intractable pruritus which is a distressing symptom. Biliary decompression and stenting can alleviate jaundice and symptoms, allowing bilirubin levels »

Table 4

Stage, clinical classification and associated survival of pancreatic cancer using the tumour (T) nodal (N) metastasis (M) staging system. (T2 = tumour > 2 cm, T3 = tumour extends beyond pancreas; T4 = tumour invades coeliac or mesenteric vessels) [56]

Stage	TNM stage	Clinical classification	Median survival (months)
IA	T1, N0, M0	Resectable	24-42
IB	T2, N0, M0	Resectable	20-26
IIA	T3, N0, M0	Resectable	15-30
IIB	T1/2/3, N0, M0	Locally advanced potentially resectable	12-21
III	T4, N0/1, M0	Locally advanced unresectable	11-14
IV	Any T, any	Metastatic	5-12

key points

SELECTED BY

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Pancreatic ductal adenocarcinoma has a very poor prognosis. The five-year survival rate for pancreatic cancer is 3% in the UK. There has been very little improvement in outcomes over the past 40 years. The combination of an aggressive disease, vague presenting symptoms and insensitive standard diagnostic tests is a key factor contributing to poor outcomes with only 15% of patients with pancreatic cancer having operable disease at diagnosis.

Although pancreatic cancer has a peak incidence in the ninth decade, 37% of patients are under 70 and 14% are under 60 years of age. In patients aged 60 and above, jaundice has a positive predictive value (PPV) of 22%, whereas other symptoms, such as abdominal pain, altered bowel habit or new-onset diabetes, are non-specific with a PPV of less than 1%. However, associated weight loss increases the PPV to between 1.5 and 2.7%.

The NICE guideline on referral for suspected cancer recommends urgent referral via a suspected cancer pathway referral if the patient is aged 40 and over with jaundice. It also recommends that an urgent direct access computerised tomography (CT) scan referral should be considered in patients aged 60 and over with weight loss and any of the following: diarrhoea; back pain; abdominal pain; nausea; vomiting; constipation; new onset diabetes.

Pancreatic cancer requires a CT scan for diagnosis. Although trans-abdominal ultrasound is excellent at detecting gallstones and confirming obstructive jaundice by the presence of bile duct dilatation, the presence of gas in the stomach makes visualisation of the pancreas poor. It is important to consider a CT scan and follow-up appointment for patients with epigastric 'dyspepsia' who have either a normal gastroscopy or symptoms that have not responded to anti-acid therapy. If the diagnosis is unclear, as can happen in autoimmune disease or chronic pancreatitis, or the tumour is unresectable, pancreatic tissue sampling can be performed using endoscopic ultrasound with fine needle aspiration.

There is an increased incidence of pancreatic cancer in a number of conditions including chronic pancreatitis (three fold) and hereditary pancreatitis (50 fold). Surveillance for pancreatic cancer is currently recommended in hereditary pancreatitis, Peutz–Jeghers syndrome and patients with a high-risk gene mutation who have a first-degree relative with pancreatic cancer. Pancreatic cysts are found incidentally on 2.6% of CT scans. Although most cysts are benign or inflammatory, there is a small risk estimated at 0.72% per year of mucinous cysts becoming malignant. Therefore, patients with a pancreatic cyst should be referred to secondary care for characterisation so that a decision can be made regarding further management, based on identified risk factors such as pancreatic duct enlargement.

to fall and reducing the risk of toxicity during subsequent chemotherapy.[35] Endoscopically placed self-expandable biliary metal stents show the best long-term results (see figure 1, p11).[36]

Because of the higher rate of complications such as pancreatic fistulae and wound leakage biliary stents in resectable disease are currently avoided unless there is a delay to surgery, if the patient is too unwell, or a stent is required as part of a clinical trial.[37] In patients with duodenal obstruction and difficult endoscopic access a percutaneous transhepatic approach can be performed to place a metal biliary stent.

The decision to proceed with biliary stenting should be discussed in the MDT meeting. Biliary stenting should not take place before an accurate pancreas protocol CT has been performed as the presence of a stent can significantly interfere with the ability of CT to stage pancreatic cancer.

Clinical and radiological evidence of duodenal obstruction requires treatment either with a radiologically placed metal duodenal stent (ideally in frail patients or in those with metastatic disease) or consideration of a gastric bypass for patients with a more favourable prognosis as duodenal stents can become blocked over time.[38]

Pain control

Pain affects approximately 80% of patients with pancreatic cancer, with half requiring stronger morphine-based drugs than codeine or tramadol. Pain is associated with poor survival, hazard ratio 1.61, as well as an impaired performance status and eligibility for chemotherapy.[39,40] Side effects of opiates may limit their use. These include sedation, constipation, confusion, tolerance and dependence, which impact negatively on quality of life. Tricyclic antidepressants and gabapentin may be used as adjunctive treatments because of their neuromodulating properties.[39]

In refractory pain, EUS coeliac plexus neurolysis can be considered as it has been shown that a 60% greater reduction in pain scores can be achieved, compared with pharmacotherapy alone, at three months. Coeliac plexus neurolysis can also lower morphine requirements by 50% and although side effects of diarrhoea, orthostatic hypotension and pain can occur they usually resolve. [41]

Nutrition and malabsorption

Approximately 80% of patients with pancreatic cancer report weight loss at the time of diagnosis and more than a third have lost > 10% of their body weight through a combination of pain, jaundice, bowel obstruction and malabsorption.[42] Specialist dietitian as well as cancer nurse support is essential to improve nutrition, function, and quality of life and also the ability to tolerate treatments.

Malabsorption because of pancreatic enzyme insufficiency occurs in more than 60% of patients with pancreatic cancer as a result of pancreatic invasion and obstruction of the pancreatic duct.[43] A faecal elastase-1 test can be used to determine exocrine pancreatic function however given the poor sensitivity of the test and significant prevalence in unresectable cancer and after pancreatic resection (74% to 92%)[43,44] guidance has suggested that enzyme replacement therapy should be offered without relying on testing.[5] The dose of enzyme needs to be titrated against symptoms and should be regularly reviewed. Proton pump inhibitors may be needed in some patients as they increase the efficacy of enzyme replacement by generating an alkaline environment in the duodenum in which enzymes are more physiologically active.

Depression

Up to 50% of patients with pancreatic cancer suffer from depression which in many develops before diagnosis.[45,46] Biological effects of the cancer can alter the action and excretion of serotonin and lower mood further which in turn augments the effects of pain, anorexia, weight loss and psychological effects of receiving information on the diagnosis, treatments and prognosis.[47] Therefore, early identification and treatment is essential although no particular antidepressant has been shown to be superior. If rapid access to psychological support is possible this should also be offered.

Diabetes

Pancreatic cancer can present with new onset diabetes or with existing type 2 diabetes worsening as the cancer progresses. Diabetes caused by loss of pancreatic function is termed type IIIc diabetes.[48]

More than half of pancreatic cancer patients have diabetes or hyperglycaemia, and the onset of diabetes typically occurs between 6 and 36 months before pancreatic cancer diagnosis in 20-25% of patients with pancreatic cancer.[49] Uncontrolled diabetes can cause polydipsia, polyuria, lethargy and weight loss diminishing quality of life.

Metformin is the recommenced oral hypoglycaemic with the addition of

insulin if required.[50] However, metformin is contraindicated in patients with significant renal or hepatic impairment and must be stopped immediately before and after CT scanning in those with renal impairment.[50]

CONCLUSION

Pancreatic cancer currently has a very poor prognosis and diagnosis is often delayed. Improvements in early diagnosis are possible with raised awareness, prompt referral or the use of direct access CT that would increase the number of patients eligible for potentially curative surgery. Research to evaluate improvements in patient pathways to earlier surgery[51] and individualised chemotherapy treatments by cancer DNA analysis are underway in the UK,[52] however currently most patients present with advanced disease. Pancreatic cancer therefore requires early liaison between dietitians, cancer nurse specialists and primary, secondary and hospice care to enable access to support for patients and their families.

Competing interests: None

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Useful information

NG85. Pancreatic cancer in adults: diagnosis and management.
www.nice.org.uk/guidance/ng85

NG12. Suspected cancer: recognition and referral
www.nice.org.uk/guidance/ng12

Pancreatic Cancer Action
https://pancreaticcanceraction.org

Pancreatic Cancer UK
www.pancreaticcancer.org.uk

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