Pancreatic cancer

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Abstract

Pancreatic cancer remains a devastating diagnosis whose prognosis has remained largely unchanged over the last two decades. Where possible, surgical resection represents the optimal treatment strategy, yet just one-fifth of patients meet the operative criteria. The non-specific nature of presentation coupled with its relative chemoresistance are partly responsible for the poor survival rates. Improvements in understanding the natural history of the disease, more sophisticated imaging techniques and increased use of endoscopic ultrasound, has allowed earlier detection and expeditious management of pancreatic cancer. The use of FOLFIRINOX and gemcitabine nab-paclitaxel regimens has shown improved median survival in patients with widespread metastatic disease. To this end, these regimens have been used with some success in the neoadjuvant setting. Future perspectives include studying the carcinogenesis of pancreatic malignancy and tumour related genetic mutations, which it is hoped will lead to new developments in the management of pancreatic cancer, and in turn improved survival rates.

Keywords Chemotherapy; genetic mutation; neoadjuvant treatment; palliative care; pancreas cancer; pancreatic ductal adenocarcinoma; surgery

Introduction

Pancreas cancer remains one of the most lethal malignant neoplasms in the developed world. In Ireland, pancreatic cancer is the 9th and 11th most common malignancy in females and males, respectively, with 564 new cases diagnosed annually. While remaining a diagnosis of the elderly with a median age at diagnosis of 74 years, the incidence of pancreatic cancer is on the increase. In the United States, a predicted 56,770 new diagnoses will be made by the end of 2019, with 45,750 deaths due to pancreatic cancer in the same year.

Despite chemotherapeutic advancements, surgical resection with R0 margins continues to be the gold standard of care. However, the vast majority of patients present with advanced malignancy thus rendering them inoperable. A deeper understanding of the pathogenesis underpinning the disease coupled with heightened public awareness has led to a number of changes in the management of pancreatic cancer. This article reviews the current management strategies employed to treat both resectable and unresectable pancreatic cancer.

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Aetiology

Pancreatic ductal adenocarcinoma (PDAC) remains the most common pancreatic malignancy, of which a number of environmental aetiological factors have been associated. Smoking, specifically tobacco carcinogen-induced production of GM-CSF, has been shown to promote malignant growth within the pancreas. A high fat, high calorie diet is known to accelerate progression of pancreatic intraepithelial neoplasia (PanIN), a known precursor of PDAC and has demonstrated increased incidence of invasive and metastatic PDAC in mouse models. Furthermore, insulin resistance and altered function of adipocytes seen in obesity have been implicated in the pathogenesis of PDAC. Obesity-induced desmoplasia has been shown not only to promote pancreatic cancer, but also to induce resistance to chemotherapy. Type 2 diabetes, often observed in overweight and obese patients, is also linked to the development of PDAC, with almost half of all patients diagnosed having concomitant type 2 diabetes mellitus. Normal blood glucose is observed in just 14% of PDAC patients. Furthermore, recent onset diabetes is frequently noted in patients with PDAC, reflecting malignancy induced β-cell dysfunction and peripheral insulin resistance.

Chronic pancreatitis is a presumed risk factor for PDAC with longstanding inflammation a reputed instigator for malignancy. While associated with increased incidence of PDAC, this association diminishes with long-term follow-up. Despite the elevated risk, screening of patients with chronic pancreatitis for the development of PDAC is not undertaken due to the low absolute risk (4% after 20 years of evolution). Furthermore, the sensitivity of imaging modalities to detect small neoplasms is limited in the remodeled parenchyma of chronic pancreatitis. While other factors have been suggested to increase the risk of developing PDAC, such as the combined oral contraceptive pill, infection with hepatitis B or C, and *Helicobacter pylori* infection, studies confirming definitive associations have yet to be undertaken.

Familial pancreas cancer accounts for 10% of all diagnoses. The International Cancer of the Pancreas Screening Guidelines published in 2013 highlighted individuals appropriate for screening as those with at least two blood relatives with pancreatic cancer. At least one affected relative should be a first-degree relative and the patient should not meet the criteria for other inherited tumour syndromes associated with increased risk of pancreatic cancer.[1]

Genetic

Both somatic and germ line mutations can play a part in the development of pancreatic cancer. Nonetheless, pancreatic tumours are highly heterogenous with some 60 genetic alterations present in any one tumour, perhaps explaining the particular potency displayed by PDAC. KRAS mutations are seen in over 90% of patients with PDAC and play a major role not only in tumour initiation but also in disease progression. Furthermore, mutations in TP53 are seen in the majority of patients with PDAC. While SMAD4 inactivation usually occurs late in the disease, when detected it is usually associated with a more aggressive phenotype.

Owing to the abundance of genomic alterations present in pancreatic malignancies, next-generation sequencing has been trialed to more accurately target individual tumour somatic mutations. Global genomic analyses have provided a new insight into pancreatic cancer genetic complexity. Whole-exome sequencing and copy number analysis have uncovered novel mutated genes including genes involved in chromatin modification (EPC1 and ARID2), DNA damage repair (ATM), axon guidance (SLIT/ROBO) and other mechanisms.[2] Furthermore, results of the recent COMPASS trial have indicated whole genome sequencing as an effective predictor of chemotherapeutic efficacy.[3]

Premalignant lesions

Pancreatic cancer has three key precursor neoplasms; intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasms (MCN).

Intraepithelial neoplasms occur following acinar to ductal metaplasia. On KRAS activation, or in some cases following pancreatic injury, acinar cells acquire a ductal phenotype resulting in non-invasive epithelial proliferations within the pancreatic ducts. These lesions are classified according to levels of increasing dysplasia as PanIN−1a, −1b, −2 and −3.

IPMNs represent a heterogenous group of cystic lesions. These are further classified into either branch duct or main duct IPMN, each with differing degrees of malignant potential. Four histologic subtypes have been described (gastric, intestinal, pancreatobiliary, and oncocytic). Branch duct IPMNs are mainly of the gastric phenotype. The intestinal type is mostly seen in main duct IPMN progressing into invasive cancer of colloid or tubular type. International consensus guidelines for the management of IPMN are shown in Figure 1.

IPMN can result in pancreatic ductal dilatation owing to mucin production and may cause pancreatitis if mucin plugs the main pancreatic duct. Development of invasive malignancy is estimated to occur in approximately 50% of patients with main duct IPMN at 5 years, compared to 15% for those with a branch duct variant. More recently, Shimizu et al. have reported a model for predicting malignancy in patients with IPMN based on cyst size, size of mural nodules and main pancreatic duct diameter.[4]

Mucinous cystic neoplasms (MCN) are large mucin-producing pre-malignant lesions of the pancreas arising mostly in the body

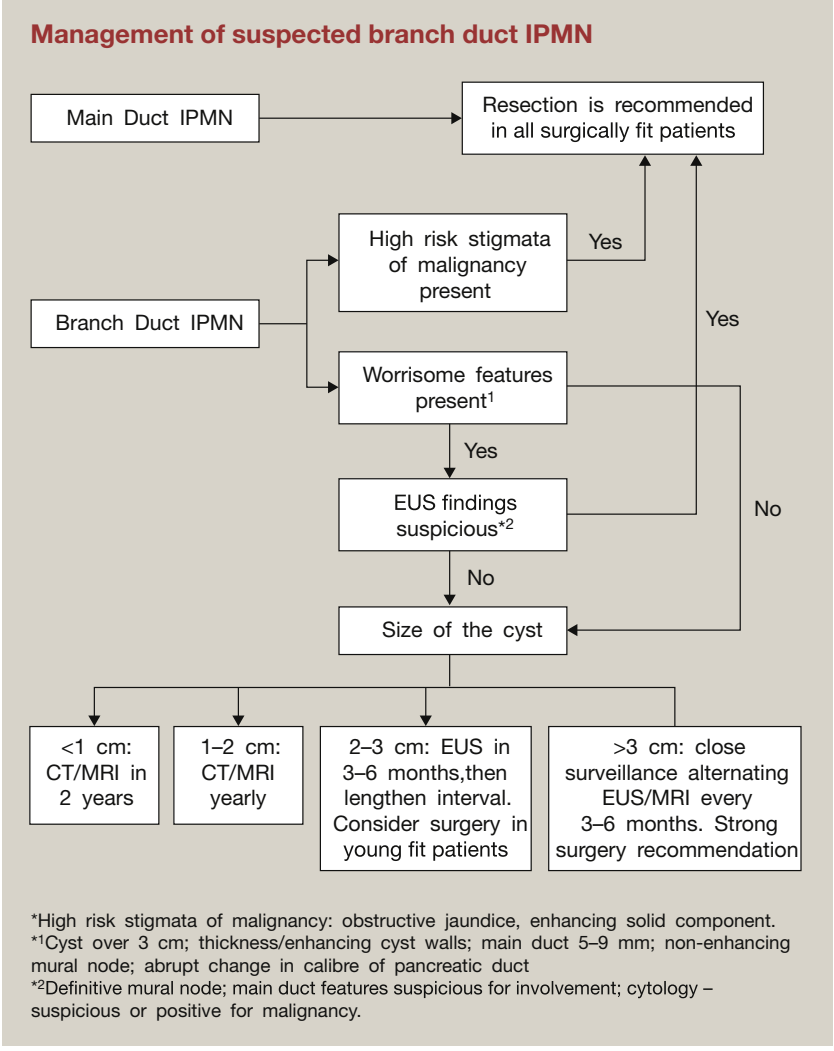

Figure 1

or tail of the gland. The median age at diagnosis is 40–50 years and they almost exclusively occur in women. MCNs are not connected with the pancreatic duct, typically are unique, unilocular or paucilocular cysts with few septations. They usually display a thick wall (>2 mm) and are surrounded by a pathognomonic ovarian-type stroma. The presence of mural nodules, a thick wall and a cyst size of over 4 cm has been proposed to predict the risk of malignant transformation, but their natural history remains ill-defined.

Diagnosis

The clinical manifestations of pancreas cancer are largely dependent on tumour location. Peri-ampullary tumours can present relatively early with obstructive jaundice, whereas the vague non-specific presenting symptoms of tumours unrelated to the bile duct undoubtedly contribute to the advanced stage of disease at diagnosis. Abdominal bloating, weight loss, early satiety and steatorrhoea are common presenting features. Pain, if present, is typically located in the epigastrium and may radiate to the back, though if present, this can indicate a poor prognosis as it is associated with neural invasion. Weight loss is usually associated with pancreatic exocrine dysfunction and malabsorption.

History and physical examination may be non-contributory; however, peri-ampullary tumours may present with Courvoisier's sign (a palpable gallbladder in the absence of gallstones). Those with metastatic disease may present with the clinical manifestations of cachexia. Haematological investigations have limited benefit. Although deranged liver function tests may be present, their diagnostic value is limited in the jaundiced patient. Carbohydrate antigen 19–9 (CA19.9), commonly used in the work up of suspected pancreatic cancer, lacks specificity and has a low positive predictive value, meaning that it is an unsuitable screening tool. Furthermore, false positivity may occur in patients with obstructive jaundice, decompensated diabetes mellitus and in smokers. Nonetheless, studies have indicated that serum levels of Ca19-9 in jaundiced patients can be indicative of an underlying malignant process, and the trend in serum Ca19-9 following biliary drainage can be predictive.[5]

Investigations

Trans-abdominal ultrasound

Trans-abdominal ultrasound is typically the initial approach in patients with jaundice. This is a relatively quick and cheap technique that is noninvasive and does not use ionizing radiation. Ultrasound can provide good views of intra and extrahepatic bile ducts and may establish the presence of gallstones. However, it is operator dependent and may not give good views of the distal common bile duct or the pancreas gland itself. This is especially true if the patient has an unfavourable body habitus.

Computed tomography and magnetic resonance imaging

Gold standard imaging remains pancreas protocol computed tomography (CT) with thin sections using both non-enhanced and late arterial (at 40–50 s) plus portal venous phases (at 65–70 s) after contrast injection. This allows visualization of tumour appearance, its size and location, and whether there is any extra pancreatic spread of disease. More importantly, this modality demonstrates the relationship of the primary tumour to the surrounding vasculature (portal vein, superior mesenteric vein, splenic vein, superior mesenteric artery, and the branches of the celiac axis). These images typically depict the tumour and any metastases as hypoattenuating during the arterial phase, with lesions best seen during the venous phase of contrast enhancement. The information obtained from CT imaging will be the key determinant in the treatment algorithm decided for the patient (Figure 2).

MRI has been shown to be equally as sensitive and specific as CT in determining resectability and metastatic dissemination of pancreatic cancer. It can be used in patients with renal impairment or in the characterization of poorly visible pancreatic lesions or indeterminate liver lesions seen on prior CT examinations. Magnetic resonance cholangiopancreatography (MRCP) is also valuable for diagnosis, and for assessing cystic lesions of the pancreas and main pancreatic duct stenosis.

Endoscopic ultrasonography (EUS)

Endoscopic ultrasound can be both diagnostic and therapeutic; however, its use in the staging of pancreatic cancer is controversial. As for transabdominal ultrasound imaging, EUS is operator dependent, which may account for the wide range of diagnostic sensitivities reported (69–94%). However, in the evaluation of smaller lesions (<2 cm), some studies have found EUS to be superior to CT. EUS is mainly used in four clinical situations: (i) in patients with negative cross-sectional evaluation

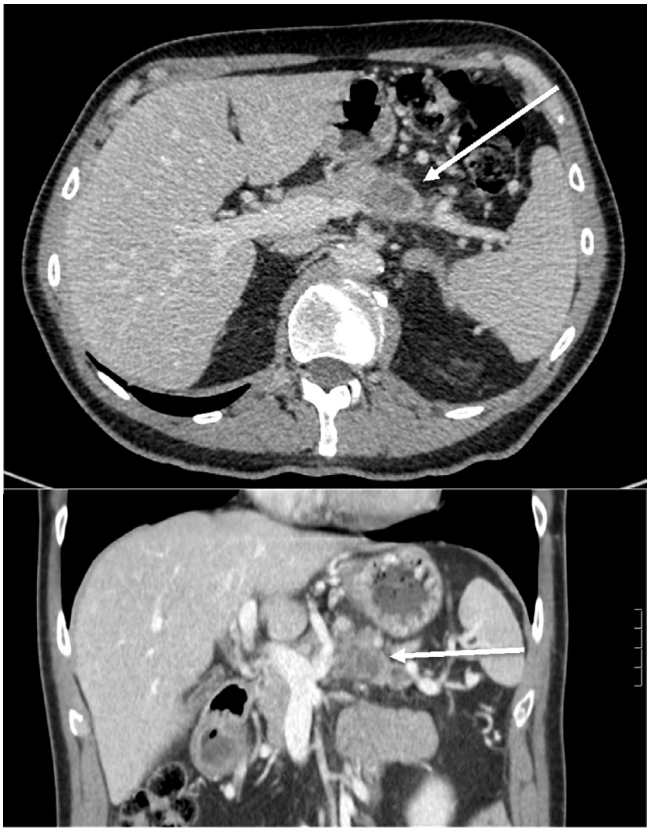

Figure 2 Axial and Coronal CT demonstrating a neoplasm (arrows) in the tail of the pancreas.

with CT or MRI when the suspicion of pancreatic cancer is high; (ii) to characterize ambiguous pancreatic lesions; (iii) to obtain pathological information in locally advanced cases; or (iv) before neoadjuvant treatment of resectable/borderline tumours when obtaining histological confirmation is essential. This broad scope of indications for EUS has lead to the technique becoming a key modality in the staging algorithm of patients with pancreatic cancer.

Endoscopic retrograde cholangio-pancreatography (ERCP)

Patients presenting with obstructive jaundice secondary to an obstructing malignant lesion of the pancreas may require ERCP. Indications for ERCP and biliary stenting are patients with resectable disease and a serum bilirubin of >150 mg/L, patients with locally advanced disease and those with unresectable or metastatic disease (Figure 3).

^{18}Fluorodeoxyglucose-positron emission tomography (FDG-PET)

Based on the premise that malignant cells have high turn-over and accelerated glucose consumption, PET is increasingly used in the staging of malignancies. Prospective studies specifically examining the utility of PET in pancreas cancer have failed to demonstrate any advantage over current imaging modalities and therefore FDG-PET is currently not recommended for routine use.

Laparoscopy

Laparoscopy in the staging of pancreatic cancer is a minimally invasive technique to establish the peritoneal spread of disease in high-risk patients. Already utilized in the staging of various malignancies, laparoscopy has the advantage of avoiding an unnecessary open exploration, thereby allowing inoperable patients to proceed directly to chemotherapy. Despite cross-sectional imaging, up to 35% of patients with pancreatic cancer are found to have occult metastatic disease at staging laparoscopy. Though not warranted in all patients, those at increased risk include patients with tumours greater than 3 cm in the head of the pancreas or those with a Ca19-9 >150 iu/l. In those with resectable disease on CT and a negative laparoscopy, it is estimated that a further 17% will have unresectable disease at laparotomy. This compares to 40% in those deemed resectable on imaging that did not undergo a staging laparoscopy prior to laparotomy.

A recent Cochrane review concluded that laparoscopic staging prevented 23 unnecessary laparotomies in 100 patients who were considered resectable by imaging alone.[6] The current consensus guidelines of the American Hepato-Pancreato-Biliary Association is that for patients with apparent resectable pancreatic cancer, staging laparoscopy should be used selectively on patients with pancreatic head tumours >3 cm, those with tumours of the pancreas body and tail, in cases with equivocal findings on CT and in patients with high CA 19.9 serum levels (>100 u/mL). Laparoscopic staging should be also be considered in patients with locally advanced pancreatic cancer that are considered candidates for local radiation treatment or experimental protocols as these patients will have an incidence of sub-radiological occult disease in approximately 35% of cases.[7]

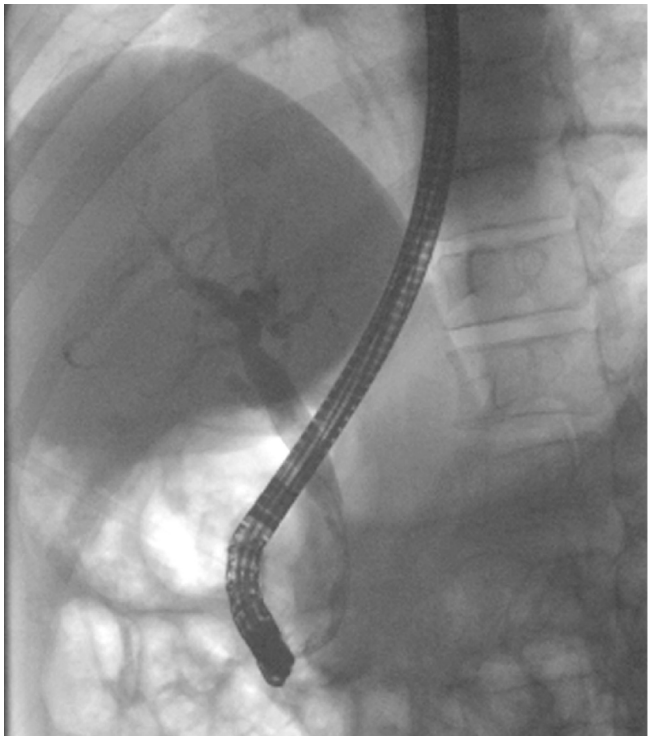

Figure 3 ERCP demonstrating proximal biliary dilatation with distal stricturing secondary to malignant neoplasm in the head of the pancreas.

Management

At diagnosis, pancreatic tumours are defined as either localized or metastatic (Table 1). Localized tumours can be further classified as resectable, borderline resectable or locally advanced unresectable tumours (Table 2). This subclassification of localized tumours facilitates multidisciplinary discussion of management strategies. In those patients with good performance status, a low comorbidity profile and upfront resectable localized disease, it remains standard practice to proceed to surgery with adjuvant chemotherapy[8] (Figure 4).

A number of centres have begun to treat upfront resectable disease with neoadjuvant therapy in the first instance, on the basis that treatment can be delivered safely allowing a period of time to assess the tumour biology. Proponents of this approach suggest it identifies the cohort of patients who progress early,

TNM classification of pancreatic tumours

Stage IA	T1, N0, M0	≤2 cm tumour, lymph nodes negative
Stage IB	T2, N0, M0	≥2 cm tumour, lymph nodes negative
Stage IIA	T3, N0, M0	Tumour beyond the pancreas, no involvement of coeliac axis or superior mesenteric artery
Stage IIB	T1-2-3, N1, M0	Resectable disease with any positive regional lymph nodes
Stage III	T4, any N, M0	Unresectable disease
Stage IV	Any T, any N, M1	Evidence of metastases

Table 1

Criteria of resectability based on the American Hepatico-Pancreatico-Biliary Association consensus report

	ARTERIAL	VENOUS
Resectable	SMA, CHA, CA clear from tumour	SMV, PV clear or ≤180° tumour contact
Borderline	SMA contact ≤180°	Tumour contacting inferior vena cava
	CHA contact, CA clear	SMV or PV contact >180°
	Variant arterial anatomy in contact with tumour affecting resectability	Thrombosis or irregularity <180° of the vein (Reconstruction possible)
Locally advance	SMA contact >180°	Unreconstructable SMV/PV occlusion
	CA contact >180°	Distal metastasis
	SMA first jejunal brach affected	

SMA, superior mesenteric artery; CHA, common hepatic artery; CA, coeliac axis; SMV, superior mesenteric vein; PV, portal vein.

Table 2

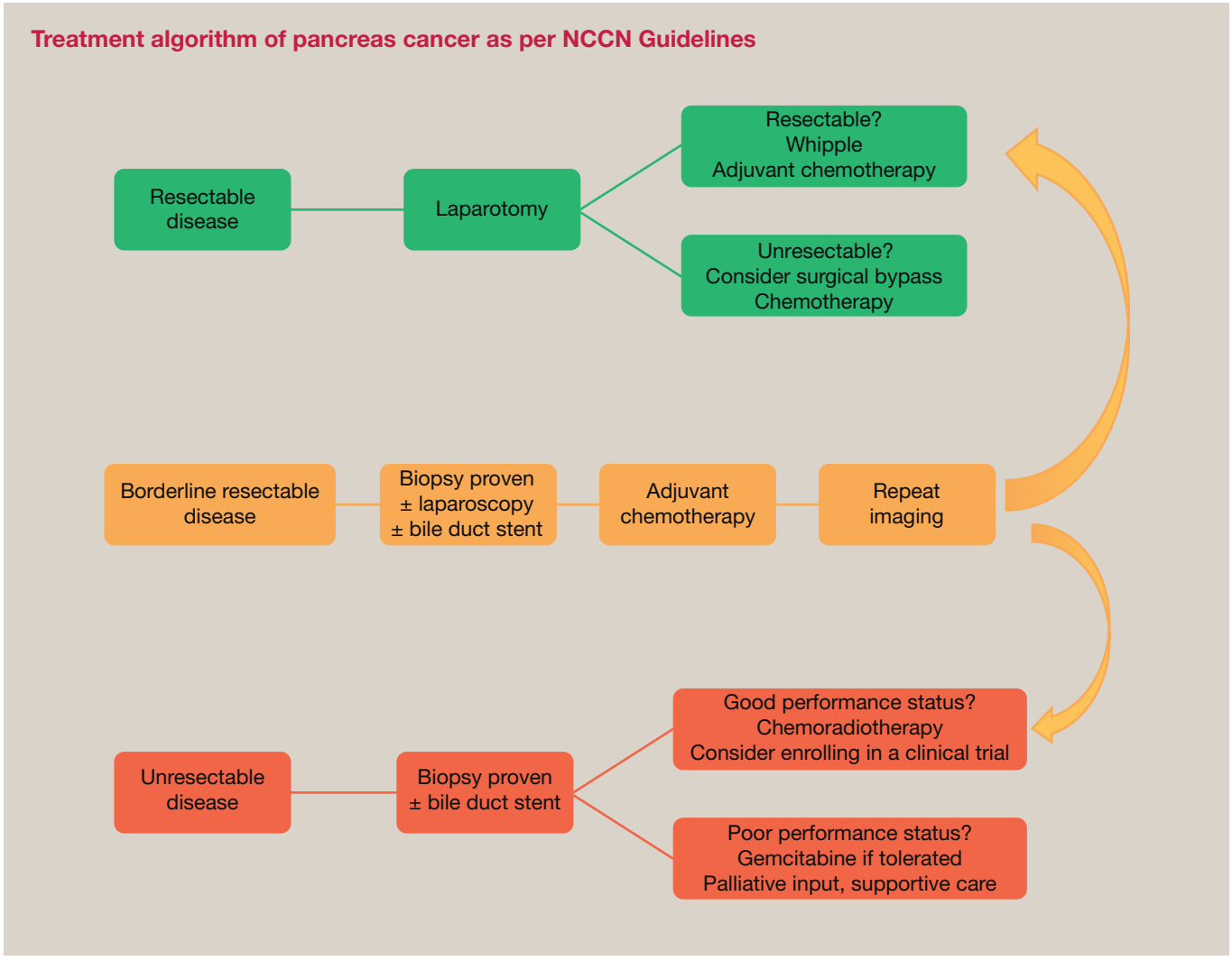

Figure 4

therefore avoiding a non-therapeutic laparotomy and may in fact result in a greater percentage of R0 resections. This was the finding of a recent meta-analysis of neoadjuvant therapy which reported that 17.8% of patients treated with neoadjuvant therapy did not proceed to surgical resection.[9] This study did demonstrate an improvement in overall survival following neoadjuvant therapy when compared to upfront resection on an intention-to-treat analysis. However, just three randomized controlled trials

were included for analysis, two of which terminated early due to poor patient accrual. Evidence from randomized controlled trials (RCTs) in this area is still lacking. A Dutch group have just completed patient accrual for their multicentre RCT[10] and a number of other RCTs looking at neoadjuvant therapy versus resection remain ongoing in Europe.[11,12]

In patients with borderline resectable disease, the National Comprehensive Cancer Network (NCCN) recommends neoadjuvant therapy, either in the form of chemotherapy or chemoradiotherapy for all fit patients. Tissue diagnosis is key prior to commencement of therapy. Neoadjuvant therapy has been shown to downstage disease and increase the number of patients resected. FOLFIRINOX combination therapy consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan, has been shown to achieve complete pathological response in 13% of cases, with 87% of borderline cases undergoing successful resection.[13] Recent publication of the first prospective RCT to evaluate neoadjuvant therapy in borderline cases showed improved 2 year and median survival following gemcitabine and radiotherapy.[14] Both FOLFIRINOX and gemcitabine regimens have been used in this setting. In the absence of a direct comparison, it is not clear which regimen is more potent as neoadjuvant therapy. Gemcitabine given with nab-paclitaxel may be more tolerable for patients given the high rate of adverse events reported following FOLFIRINOX administration.

Surgery

Pancreaticoduodenectomy or a Whipple's procedure is the standard surgical approach for tumours in the head of the pancreas. This includes resection of the duodenum, gallbladder, bile duct and head of the pancreas with peri-pancreatic lymphatics (Figure 5) and can be performed by open, laparoscopic, or as more recently described, a robotic approach. Surgery may also involve an antrectomy in the case of a 'classic' Whipple, or the pylorus may be left in situ in the case of 'pylorus-preserving' pancreaticoduodenectomy. In patients who have undergone neoadjuvant treatment, it may be difficult to differentiate focal tumour infiltration of the vessels (superior mesenteric vein, portal vein, superior mesenteric artery) from treatment related fibrosis. The achievement of an R0 resection is paramount for patient outcome, therefore many adopt a radical approach to vein resection during a Whipple procedure, as current data indicates similar outcomes for patients even with vein resection if R0 margins are obtained.

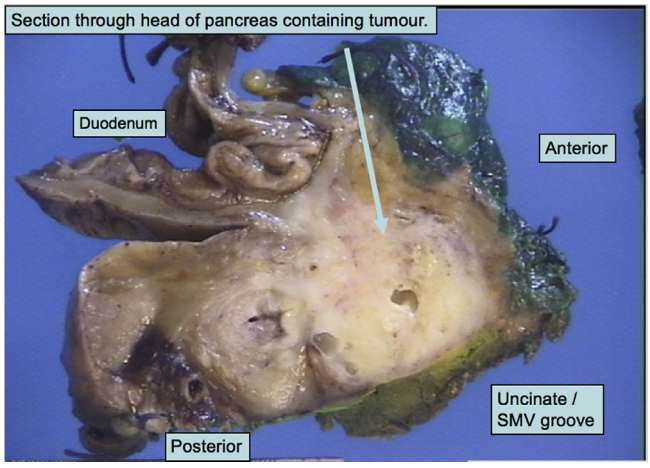

Figure 5 Sagittal section of pancreaticoduodenectomy resection specimen.

Adjuvant therapy

Adjuvant treatment is recommended for all patients following R0/R1 resection, to commence within 12 weeks of surgery. Current NCCN guidelines advocate adjuvant treatment even for those following neoadjuvant therapy, to complete a total of 6 months of treatment. Either gemcitabine as monotherapy or 5-FU/leucovorin are recommended, with the ESPAC-3 trial showing equivalent median overall survival of 23.6 and 23 months for gemcitabine and 5-FU, respectively. While this trial failed to demonstrate a survival benefit, gemcitabine was better tolerated than 5-FU with significantly more patients complaining of grade 3–4 toxicity following 5-FU treatment. More importantly, this trial demonstrated the importance of chemotherapy completion, with failure to complete shown as an independent prognostic factor for poorer overall survival. The more recently published ESPAC-4 trial compared gemcitabine monotherapy to gemcitabine/capecitabine in combination. Combination treatment was associated with a significantly improved median overall survival of 28 months compared to 25.5 months with monotherapy.[15] Furthermore, results of the CONKO-005 trial published last year failed to demonstrate any benefit with the addition of erlotinib (an EGFR inhibitor) to gemcitabine.[16]

Regionalization of care

Following Birkmeyer's work highlighting the association between surgical volume and postoperative outcomes, a number of malignancies have now been centralized to large volume academic centers. Pancreatic cancer is one such malignancy where, throughout Europe a number of groups have published improved postoperative outcomes following centralization. The Dutch pancreas group have reported not only a reduction in their perioperative mortality following pancreaticoduodenectomy but also an increase in the number of patients being resected and improved overall survival in high volume centres.[4] Similarly, Yoshioka and colleagues in Japan have shown a clear association between increased surgeon volume and reduced perioperative mortality and length of stay following a Whipple's procedure.[17]

The reasons for this improvement are multifactorial and cannot just be attributed to surgeon volume alone. The multidisciplinary infrastructure present in large academic centers is key to the improved postoperative outcomes described, including specialized anesthetists, radiologists and oncologists along with established postoperative care pathways present in high-dependency and intensive care units. Furthermore, high-volume centers are more equipped to recognize and manage postoperative complications.

However, patients presenting with resectable disease still represent just 20% of all diagnoses of pancreas cancer. The vast majority of patients will present with either locally advanced or metastatic disease. For these patients it remains unclear as to whether the centralization of pancreas cancer services has improved their management, or indeed their survival.

Metastatic disease

Depending on the presentation of the patient, symptomatic control may need to be established prior to the commencement of chemotherapy. Obstructive jaundice is the presenting complaint in up to 75% of patients with a pancreas tumour, and needs to be relieved prior to the commencement of palliative treatment. Once a tissue diagnosis has been made, placement of a covered metallic stent is favored over a plastic stent as it is associated with a lower incidence of cholangitis and rarely requires replacement (Figure 6). When the bile duct cannot be cannulated endoscopically, percutaneous drainage is an option, with subsequent internalization to provide palliation. Though not our preferred approach, patients may also undergo surgical bypass of the obstructing lesion. While a number of meta-analyses have found equivalent outcomes comparing endoscopic, percutaneous and surgical biliary bypass, there is an increased length of stay and peri-procedural morbidity associated with surgical biliary bypass.

Up to one-quarter of patients develop gastric outlet obstruction as a consequence of a pancreas tumour. In symptomatic patients with widespread metastatic disease, advanced age or multiply comorbidity, endoscopic stent placement should be considered in the first instance. In those who have a limited disease burden, minimal comorbidities or in whom an endoscopic stent is not technically feasible, an open or laparoscopic surgical bypass will provide effective symptomatic relief.

Patients with metastatic pancreatic cancer, a good performance status and adequate biliary drainage should be offered palliative chemotherapy in the form of 5FU/leucovorin in addition to oxaliplatin and irinotecan (FOLFIRINOX). A potentially less toxic alternative that may be better tolerated is gemcitabine with nab-paclitaxel and this regimen has been shown to improve median survival in patients with metastatic disease. A limited amount of data supports a potential survival benefit for second-line chemotherapy compared to best supportive care alone. The decision to pursue second line treatment should be made on a case by case basis, with the importance of supportive care emphasized.

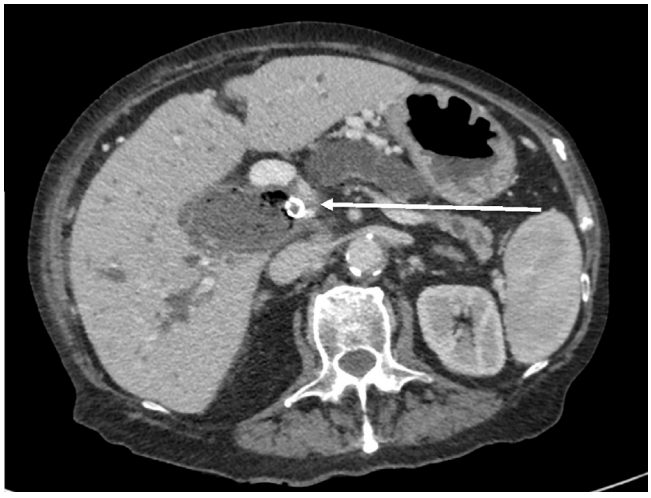

Figure 6 Axial CT post ERCP and metal stent insertion (arrowed). Persistent intrahepatic biliary duct dilatation is seen.

Follow-up

Follow up of patients with pancreatic cancer following resection is key, not just to detect signs and symptoms of disease recurrence but also to assess pancreas endocrine and exocrine insufficiency. After pancreaticoduodenectomy, up to 75% patients suffer exocrine dysfunction and 25% develop diabetes mellitus, and therefore close collaboration with a dietician is essential. Guidelines recommend clinical review of patients at regular 3–6 monthly intervals for the first 2 years postoperatively. In the absence of worrying features, CT with Ca 19-9 should be performed on an annual basis. Patients who develop recurrent disease should have oncology referral and be considered for palliative chemotherapy.

Future directions

Pancreatic cancer remains a devastating disease with a guarded prognosis for newly diagnosed patients. Despite this, a number of new developments in understanding the tumour biology have led to more daring treatment options, especially in patients with borderline resectable disease. Furthermore, the improvement in chemotherapeutic interventions has shown longer survival rates than before, even in patients not deemed operable. Perhaps the most exciting of all recent developments is that next-generation sequencing may hold the key to a refined understanding of pancreatic ductal adenocarcinoma. It is these sustained efforts that will forge an improved clinical course for patients with pancreatic cancer. ◆

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