

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2021 June 15; 13(6): 462-637



**OPINION REVIEW**

- 462 Efficacy and safety of endoscopic resection in treatment of small gastric stromal tumors: A state-of-the-art review  
*Chen ZM, Peng MS, Wang LS, Xu ZL*

**REVIEW**

- 472 Current controversies and advances in the management of pancreatic adenocarcinoma  
*Zeeshan MS, Ramzan Z*
- 495 Familial adenomatous polyposis and changes in the gut microbiota: New insights into colorectal cancer carcinogenesis  
*Biondi A, Basile F, Vacante M*
- 509 Application of the woodchuck animal model for the treatment of hepatitis B virus-induced liver cancer  
*Suresh M, Menne S*

**MINIREVIEWS**

- 536 Application of metabolomics in clinical and laboratory gastrointestinal oncology  
*Gao P, Huang X, Fang XY, Zheng H, Cai SL, Sun AJ, Zhao L, Zhang Y*
- 550 Targeting of elevated cell surface phosphatidylserine with saposin C-dioleoylphosphatidylserine nanodrug as individual or combination therapy for pancreatic cancer  
*Davis HW, Kaynak A, Vallabhapurapu SD, Qi X*
- 560 Current indications for endoscopic submucosal dissection of early gastric cancer  
*Zheng Z, Yin J, Liu XY, Yan XS, Xu R, Li MY, Cai J, Chen GY, Zhang J, Zhang ZT*
- 574 Poly adenosine diphosphate-ribosylation, a promising target for colorectal cancer treatment  
*Jeong KY, Park M*

**ORIGINAL ARTICLE****Retrospective Study**

- 589 Yield of surgery in solid pseudopapillary neoplasms of the pancreas: A case series and literature review  
*Silano F, de Melo Amaral RB, Santana RC, Neves VC, Ardengh JC, do Amaral PCG*

**Observational Study**

- 600 Serum vascular endothelial growth factor as a tumor marker for hepatocellular carcinoma in hepatitis C virus-related cirrhotic patients  
*Alzamzamy A, Elsayed H, Abd Elraouf M, Eltoukhy H, Megahed T, Aboubakr A*

**Prospective Study**

- 612** Gastrointestinal function testing model using a new laryngopharyngeal pH probe (Restech) in patients after Ivor-Lewis esophagectomy

*Babic B, Müller DT, Gebauer F, Schiffmann LM, Datta RR, Schröder W, Bruns CJ, Leers JM, Fuchs HF*

**SYSTEMATIC REVIEWS**

- 625** Current role of hepatopancreatoduodenectomy for the management of gallbladder cancer and extrahepatic cholangiocarcinoma: A systematic review

*Fancellu A, Sanna V, Deiana G, Ninniri C, Turilli D, Perra T, Porcu A*

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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**INDEXING/ABSTRACTING**

The *WJGO* is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJGO* as 2.898; IF without journal self cites: 2.880; 5-year IF: 3.316; Ranking: 143 among 244 journals in oncology; Quartile category: Q3; Ranking: 55 among 88 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2019 is 2.0 and Scopus CiteScore rank 2019: Gastroenterology is 86/137.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Ya-Juan Ma.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Oncology*

**ISSN**

ISSN 1948-5204 (online)

**LAUNCH DATE**

February 15, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Rosa M Jimenez Rodriguez, Pashtoon Kasi, Monjur Ahmed, Florin Burada

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

**PUBLICATION DATE**

June 15, 2021

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Current controversies and advances in the management of pancreatic adenocarcinoma

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**Author contributions:** Zeeshan MS was responsible for collecting reference articles, manuscript writing and figure/table generation; Ramzan Z provided expertise in the field of gastrointestinal endoscopy, manuscript writing and editing, and designing the aims of the manuscript.

**Conflict-of-interest statement:**

Authors declare no conflict of interest for this article.

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**Manuscript source:** Invited manuscript

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### Abstract

Pancreatic adenocarcinoma is a lethal disease with a mortality rate that has not significantly improved over decades. This is likely due to several challenges unique to pancreatic cancer. Most patients with pancreatic cancer are diagnosed at a late stage of disease due to the lack of specific symptoms prompting an early investigation. A small subset of patients who are diagnosed at an early stage have a better chance at survival with curative surgical resection, but most patients still succumb to the disease in a few years. The dismal overall prognosis is due to suspected micro-metastasis at an early stage. Due to this reason, there is a recent interest in treating all patients with pancreatic cancers with systemic therapy upfront (including the ones that are surgically resectable). This approach is still not the standard of care due to the lack of robust prospective data available. Recent advancements in treatment regimens of chemotherapy, radiation and immunotherapy have improved the overall short-term survival but the long-term survival still remains poor. Novel approaches in diagnosis and treatment have shown promise in clinical studies but long-term clinical data is lacking. The following manuscript presents an overview of the epidemiology, diagnosis, staging, recent advances, novel approaches and controversies in the management of pancreatic adenocarcinoma.

**Key Words:** Pancreatic adenocarcinoma; Advances in management; Imaging; Novel approaches; Chemotherapy; Controversies

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**Core Tip:** Early diagnosis and treatment of pancreatic adenocarcinoma has remained a challenge over the last several decades. Despite best efforts, the long-term survival rate has not significantly improved. The following manuscript highlights the current

**Specialty type:** Oncology**Country/Territory of origin:** United States**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
 Grade B (Very good): B, B  
 Grade C (Good): 0  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** January 8, 2021**Peer-review started:** January 8, 2021**First decision:** February 24, 2021**Revised:** March 22, 2021**Accepted:** May 25, 2021**Article in press:** May 25, 2021**Published online:** June 15, 2021**P-Reviewer:** Mu PY**S-Editor:** Fan JR**L-Editor:** A**P-Editor:** Li JH

advances and controversies in the management of pancreatic cancer. The standard systemic therapies have been presented in a format that is easy to read and follow. Novel approaches in diagnosis and management have been discussed in light of evidence-based medicine.

**Citation:** Zeeshan MS, Ramzan Z. Current controversies and advances in the management of pancreatic adenocarcinoma. *World J Gastrointest Oncol* 2021; 13(6): 472-494

**URL:** <https://www.wjgnet.com/1948-5204/full/v13/i6/472.htm>

**DOI:** <https://dx.doi.org/10.4251/wjgo.v13.i6.472>

## INTRODUCTION

Pancreatic cancer ranks as the fourth leading cause of cancer related death in the United States and seventh leading cause of cancer deaths worldwide[1]. Approximately 57600 patients are diagnosed with pancreatic cancer annually[2], with a vast majority of these patients dying within the first year of diagnosis. The incidence of pancreatic cancer in the United States is 1.3 times higher in males than females[3]. There is a slightly increased risk in blacks than in whites[4]. Several other risk factors for pancreatic cancer have been identified[5], such as cigarette smoking[6,7], physical inactivity and obesity[8], high intake of saturated fat and/or processed or smoked meats[9], family history and genetic predisposition syndromes[10-12], nonhereditary chronic pancreatitis[13,14], and presence of pancreatic cysts such as intraductal papillary mucinous neoplasm of pancreas[15]. Due to high mortality of pancreatic cancer, many studies have looked at the prognostic indicators and predictors of mortality[16-19]. Several new modalities have been introduced in diagnosis and management of pancreatic cancer over the past few decades[20] but overall prognosis still remains poor[2].

## PATHOLOGY

The most common type of pancreatic cancer is pancreatic adenocarcinoma, representing approximately 85% of all pancreatic neoplasms. Unfortunately, this accounts for the most aggressive type of pancreatic cancer with the poorest prognosis overall (Figure 1). Neoplasms arising from the endocrine pancreas (such as pancreatic neuroendocrine tumors) account for approximately 5% of all pancreatic tumors. Other rare tumors include acinar carcinoma, cystic neoplasms (mucinous cystadenoma, intraductal papillary mucinous tumors, solid pseudopapillary tumors, serous cystadenoma), metastatic tumors, *etc.*

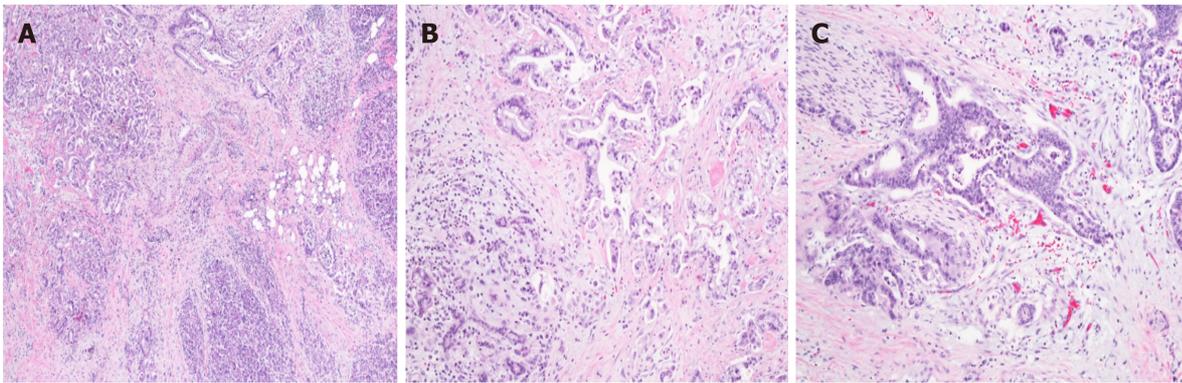
## CLINICAL PRESENTATION

The presentation of pancreatic cancer varies by the location of the tumor. Tumors located in the head of pancreas (approximately 60%-70%) usually present with painless jaundice[21] due to obstruction of the intra-pancreatic portion of distal common bile duct. Other symptoms include steatorrhea and weight loss. On the other hand, tumors in the body of pancreas (20%-25%) present somewhat late in the disease course with severe abdominal/back pain, anorexia and weight loss.

Rarely, a pancreatic mass is found as an incidental finding on computed tomography (CT) scan performed for another reason. Overall incidence of an incidental pancreatic mass over an eight year period in one study was reported as 7%, with one half of these were adenocarcinoma[22].

## DIAGNOSTIC EVALUATION

Symptoms alone are not sensitive to diagnose pancreatic cancer as many other



**Figure 1 Hematoxylin and eosin stains**[21]. A: Hematoxylin and eosin stains of normal and adjacent ductal adenocarcinoma 40 ×; B: demonstrates invasive adenocarcinoma (100 ×); C: Perineural invasion is demonstrated. Citation: Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jariod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; 7: 189-197. Copyright© The Authors 2005. Published by Springer Nature.

diseases can present with similar symptoms[23]. Initial workup starts with simple blood tests and cross-sectional imaging, followed by additional testing based upon clinical presentation.

### **Blood tests**

For patients suspected to have a mass in the head of pancreas causing biliary obstruction, initial blood work should include liver function tests (such as serum aminotransferases, alkaline phosphatase, and bilirubin). Evidence of cholestasis (elevation of alkaline phosphatase and bilirubin) could suggest obstruction of distal common bile duct in the right clinical scenario. Serum amylase and lipase can be checked to rule out acute pancreatitis in patients with severe epigastric pain but is not useful to diagnose pancreatic cancer.

### **Abdominal ultrasound**

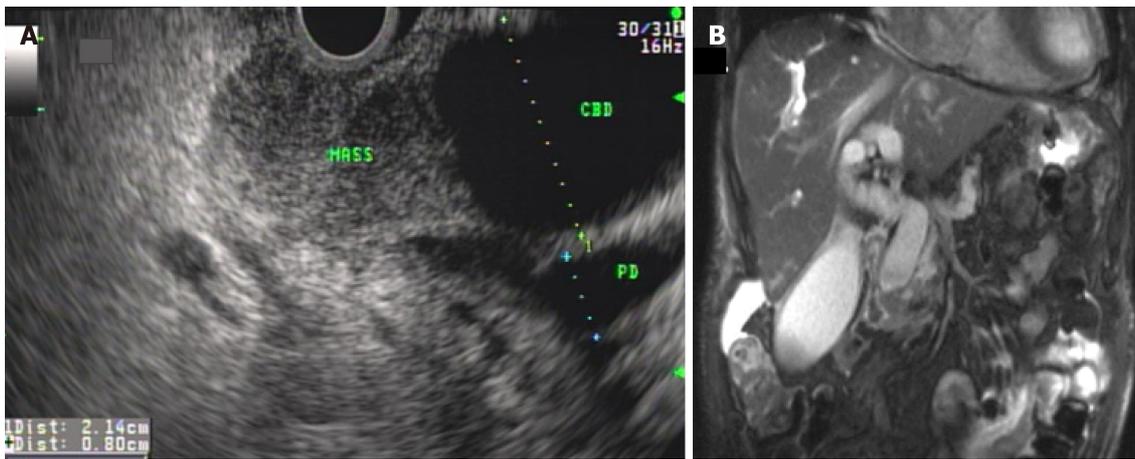
The most important test in the diagnosis of pancreatic cancer is diagnostic imaging. Abdominal ultrasound is inexpensive, readily available and useful in certain clinical situations. It helps determine the presence of bile duct dilation, large masses in the head of pancreas (> 3 cm), any liver metastasis, ascites, *etc.* However, it has several limitations. It is not useful in the evaluation of the entire pancreas, as the retroperitoneal location of pancreas and overlying gas in the stomach and small intestine can obscure visualization of the entire pancreas.

### **Abdominal CT scan**

The most useful test in diagnosing a pancreatic mass is abdominal CT scan. A special dedicated pancreas protocol CT scan [triple phase, helical, contrast enhanced, multidetector row CT with three dimensional reconstruction; multidetector computed tomography (MDCT)] has a sensitivity of 89%-97% [24-26]. The classic appearance of an exocrine pancreatic cancer is a poorly defined hypoattenuating mass within the pancreas, although isoattenuation can be seen in smaller tumors[27]. Other abnormalities may include abrupt cut off of pancreatic duct with proximal (upstream) pancreatic duct dilation, pancreatic atrophy, *etc.* Masses in the head of pancreas and ampulla can cause dilation of the bile duct and pancreatic duct (double duct sign)[28]. A good quality (pancreas protocol) CT also helps in the staging of tumors, which can range from delineating vascular anatomy in early-stage disease to evaluating distant metastasis in stage IV disease[29-31].

### **Magnetic resonance cholangiopancreatography**

Magnetic resonance cholangiopancreatography (MRCP) creates a three-dimensional image of the pancreaticobiliary tree, liver and adjacent vascular structures. It is especially useful in outlining the pancreatic duct and biliary duct, obviating the need for having to inject dye during endoscopic retrograde cholangiopancreatography (ERCP) to obtain that information[32] (Figure 2). Moreover, subtle strictures, partly cystic masses and intrahepatic masses can be delineated with addition of contrast enhanced (gadolinium) injection during magnetic resonance imaging (MRI) of the abdomen. MRCP provides a road map in difficult situations such as patients with



**Figure 2 Malignant biliary obstruction from mass in the head of pancreas causing common bile duct and pancreatic duct dilation (double-duct sign) on endoscopic ultrasound and magnetic resonance cholangiopancreatography[21].** A: Endoscopic ultrasound; B: Magnetic resonance cholangiopancreatography, note the distended gallbladder, seen in patients with malignant biliary obstruction (Courvoisier's sign). Citation: Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jariod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; 7: 189-197. Copyright© The Authors 2005. Published by Springer Nature.

altered surgical anatomy (*e.g.*, Bilroth II, Roux-en-Y gastric bypass, *etc.*), gastric or duodenal stenosis, bile duct obstruction in setting of chronic pancreatitis, *etc.*[33]. Despite the value of MRI/MRCP in certain clinical situations, MRI does not offer significant advantage over MDCT in routine workup of pancreatic cancer[34-36], except probable increased sensitivity for detecting small liver metastasis[37-40].

#### Tumor markers

The role of tumor markers in diagnosing pancreatic cancer is controversial. The most useful and widely used tumor marker is cancer associated antigen 19-9 (CA 19-9). The reported sensitivity ranges from 70%-92% and specificity ranges from 68%-92%[41]. There are several caveats of using CA 19-9 in diagnosis of pancreatic cancer. The sensitivity is lower for smaller tumors[41,42]. In patients with a Lewis negative phenotype (approximately 5%-10% of the population), CA 19-9 is not a useful tumor marker[43,44]. The specificity is low as it is frequently elevated in patients with other cancers and various benign pancreaticobiliary tumors[44-46]. Due to low positive predictive value of CA 19-9, it is not used as a screening test for pancreatic cancer[47]. Nevertheless, there are two distinct advantages of using CA 19-9 in patients with pancreatic cancer. Firstly, it has some value as a prognostic marker, *i.e.*, a markedly elevated CA 19-9 likely signifies occult metastasis and hence, poor overall prognosis [48-51]. Secondly, it is useful in monitoring disease activity during treatment. For example, elevation in CA 19-9 Levels after curative surgical resection may indicate early cancer recurrence even before appearance of radiographic abnormality on surveillance imaging[52-54].

#### Endoscopic ultrasound

The diagnosis of pancreatic cancer is made on histological confirmation of biopsy specimens. The best modality to obtain tissue diagnosis is Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) of the pancreatic mass (Figure 2). The entire pancreas can be evaluated through the stomach and duodenum with the help of EUS. A special needle can be advanced through the wall of the upper gastrointestinal tract into the pancreatic mass without risking spread of cancer cells into the peritoneum as is seen with US or CT guided aspiration. The sensitivity and specificity of EUS-FNA has been reported at 89%-92% and 96% respectively[55,56]. Several advantages of EUS-FNA over US or CT guided approach (other than superior accuracy) include less risk of needle tract seeding[57], less risk of peritoneal seeding[58], ability to perform local staging, and cost[59]. Limitations of EUS are that it is operator dependent and it is suboptimal for evaluation of distant metastasis.

As an imaging tool, EUS is very sensitive and is commonly used in screening patients-with familial pancreatic cancer or other hereditary syndromes[60]. EUS not only helps biopsy the tumor but also provides simultaneous access to sampling of regional nodes, -ascites, liver lesions and malignant cyst fluid. Moreover, it helps

assess resectability of tumor during diagnostic evaluation (Figure 3). Additionally, recent studies have explored the utility of EUS in many other sophisticated ways, such as injection of cytotoxic agents, application of radiofrequency ablation to ablate neoplastic lesions, introducing instruments directly into the lesions for diagnostic purposes, *etc.*

Despite overwhelming evidence to support the utility of EUS in evaluation of pancreatic cancer, there are certain limitations and challenges in its use. In certain situations, masses in setting of focal chronic pancreatitis (with focus of ductal adenocarcinoma) and/or autoimmune pancreatitis can be indistinguishable from pancreatic cancer and hence, pose a clinical challenge in diagnosis and management of these lesions. In these difficult situations, a multimodality approach involving clinical history (*i.e.*, lack of alarm symptoms), radiological interpretation and short term follow up may be necessary. Additionally, certain technical limitations of EUS include difficulty in accessing tumors in the uncinate process of pancreas due to acute angulation in the second portion of duodenum, as well as the inherent limitations in obtaining rich aspirate with small FNA needles. The introduction of new and better needles such as fine needle biopsy needles with different designs and compositions have largely solved these problems. Despite these rare challenges and limitations, in the hands of experts, EUS imaging and sampling is very accurate and considered the gold standard in detecting and diagnosing pancreatic cancer.

Centers without personnel experienced with EUS-FNA rely on percutaneous biopsy of pancreatic masses to establish a diagnosis. Potential disadvantages of CT guided percutaneous biopsy approach include malignant seeding of the needle tract, though this theory has not been proven convincingly.

### **ERCP**

ERCP is a useful tool in evaluating the duodenum, ampulla, biliary and pancreatic system. In addition to direct visualization, ERCP can help obtain tissue samples for diagnosis, such as brush samples of indeterminate strictures for cytology, as well as intraductal biopsies. As ERCP has potential risks such as bleeding, perforation and pancreatitis, it is generally not considered the initial test for the diagnosis of suspected pancreatic cancer. EUS is still considered the gold standard in obtaining samples for tissue diagnosis. However, ERCP has great clinical utility in relieving malignant biliary obstruction by stent placement (Figure 4).

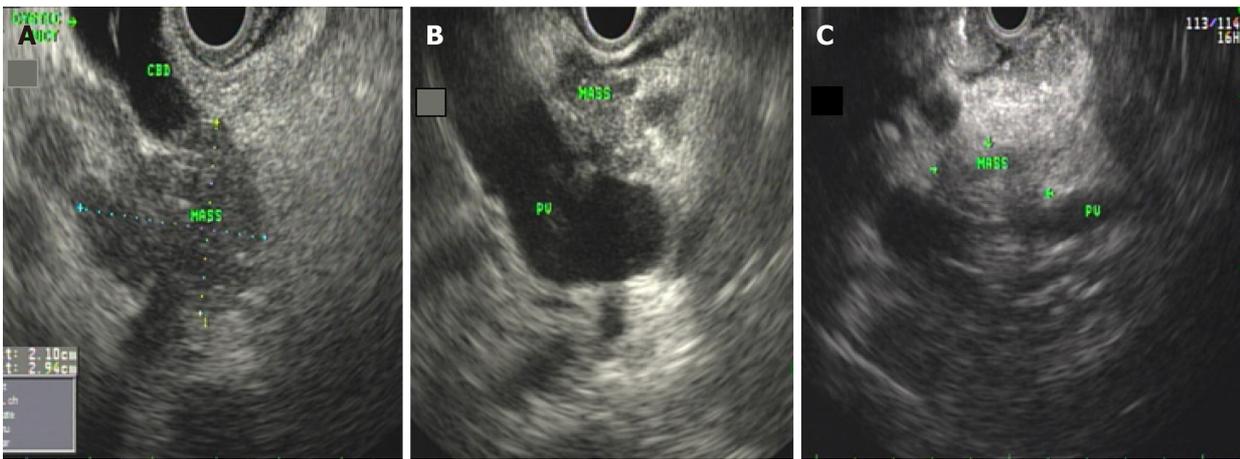
### **Positron emission tomography scan**

The role of positron emission tomography (PET) scan in routine staging of pancreatic cancer is controversial. Studies have shown data supporting the utility of PET scan in staging of pancreatic cancer[61-63], whereas other studies have shown conflicting results[64,65]. Use of 18F-fluorodeoxyglucose (FDG) PET combined with CT (PET/CT) and MRI (PET/MRI) has generated interest in diagnosis, staging (lymph node involvement and metastasis)[66], assessment of pathological grade[67], assessment of treatment response, planning of radiation treatment, *etc.*[68-70]. There are certain advantages of PET/MRI over PET/CT such as lower radiation dose and superior soft tissue contrast[68]. However, the subgroup of patients with pancreatic cancer who will benefit from PET/CT or PET/MRI is not clearly understood. Hence, PET scan is not used routinely but only in certain select situations as illustrated in National Comprehensive Cancer Network and European Society for Medical Oncology guidelines[71].

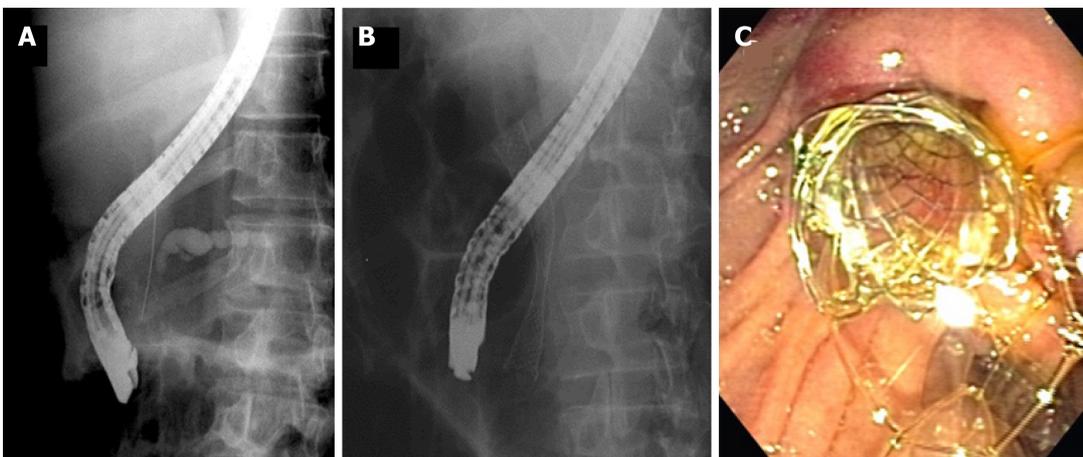
### **Staging laparoscopy**

The role of staging laparoscopy has evolved over time. The utility of staging laparoscopy relies on the pretext that small occult metastatic lesions can be missed by the available diagnostic imaging modalities and can be picked up by diagnostic laparoscopy. Hence, in certain clinical situations where the pre-test clinical probability of occult metastatic disease is high, staging laparoscopy can detect small sub-cm metastatic lesions on the peritoneum and surface of the liver and upstage the disease from resectable to stage IV metastatic disease. This also helps in re-directing the focus to palliative chemotherapy rather than neoadjuvant treatment in preparation for eventual needless surgical resection. Ideal candidates who may benefit from diagnostic laparoscopy include large tumors (> 3 cm), tumors in the body and tail of pancreas, elevated CA 19-9 > 1000, locally advanced but resectable disease, imaging suspicious for occult metastatic disease, *etc.*[72-74].

Routine use of laparoscopic ultrasound during staging laparoscopy has the potential of finding small metastatic lesions that can be missed by routine cross-sectional imaging or visual inspection during laparoscopy. When used in conjunction with



**Figure 3 Endoscopic ultrasound images**[21]. A: Endoscopic ultrasound (EUS) images of pancreatic adenocarcinoma invading the distal common bile duct; B: EUS images of pancreatic adenocarcinoma invading the portal vein; C: EUS images of pancreatic adenocarcinoma invading the portal vein confluence. Citation: Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jarrod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; 7: 189-197. Copyright© The Authors 2005. Published by Springer Nature.



**Figure 4 Malignant pancreatic stricture causing upstream pancreatic duct dilation**[21]. A: Note that the wire was advanced into the bile duct during endoscopic retrograde cholangiopancreatography to place a biliary stent for palliation of obstructive jaundice; B and C: Placement of a metallic biliary stent for palliation of obstructive jaundice in a patient with unresectable pancreatic cancer [fluoroscopic picture (B); endoscopic picture (C)]. Citation: Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jarrod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; 7: 189-197. Copyright© The Authors 2005. Published by Springer Nature.

laparoscopy, laparoscopic ultrasound can help in evaluation of primary tumors, peripancreatic vascular anatomy, detect small occult metastatic lesions and hence, change the surgical approach and prevent unnecessary radical surgery[75-79].

## NOVEL DIAGNOSTIC IMAGING MODALITIES

Several studies in the last decade have sparked an interest in novel mucosal imaging, but none has yet been accepted as a routine investigation in the evaluation of suspected pancreatic mass. Narrow band imaging technology uses light of specific blue and green wavelengths to augment certain mucosal features while visualizing the wall of pancreatic duct (with a small catheter inserted into the pancreatic duct) ('pancreatoscopy')[80].

Optical endomicroscopy permits imaging of the lining of pancreatic duct and wall of pancreatic cyst with the help of a small diameter probe introduced into the pancreatic duct at the time of EUS or ERCP. Such sophisticated imaging has a potential to increase diagnostic yield of sampling by targeted biopsies in the high yield area.

Two imaging technologies used in this manner include confocal laser endomicroscopy [81,82] and high resolution microendoscopy[83]. Other imaging modalities such as optical coherence tomography have even lower clinical applicability as it employs infrared light to scan a few millimeters beneath the lining of the duct making it a time consuming and a low yield test[84-86].

Intraductal ultrasound (IDUS), a mini-ultrasound probe, can be used to evaluate indeterminate strictures. It is introduced within the pancreatic duct which makes it more invasive. In some studies it has been found to be useful in evaluation of early pancreatic cancers and determine margins of malignant cystic lesions such as intraductal papillary mucinous neoplasms before surgical resection[87]. IDUS is not commonly used in the United States due to limited clinical application and risk of pancreatitis associated with the procedure[88]. On the other hand, contrast enhanced EUS, which utilizes intravenous contrast to enhance a pancreatic lesion has been received with more interest in recent times[89]. In a meta-analysis, the pooled sensitivity of contrast-enhanced EUS for the differential diagnosis of pancreatic adenocarcinomas was 94% (95%CI: 0.91-0.95), and the specificity was 89% (95%CI: 0.85-0.92)[90].

Another modality using EUS, EUS elastography, helps distinguish between benign focal mass in chronic pancreatitis from pancreatic cancer by performing quantitative analysis of tissue stiffness. In one study, the sensitivity and specificity for detecting pancreatic malignancies were 100% and 92.9% respectively[91]. Three-dimensional reconstruction and spectrum analysis using EUS has shown -good results, and has the potential to be used more often in the future[92].

As pancreatic cancer has the potential to cause micro metastasis even in early stage of disease, research has been carried out to determine the molecular profiling of these tumors. Imaging agents such as peptides that bind to specific factors on the surface of pancreatic tumors have been developed and include: cathepsin E, integrin  $\alpha_v\beta_6$ , plectin 1, claudin-4 and oncolytic adenovirus mutant[92-97]. Similarly, engineered biological agents such as oncolytic adenovirus have shown efficacy and tumor selectivity in preclinical pancreatic cancer models[98,99]. More robust clinical studies are needed before it can be used in routine evaluation of early pancreatic cancer.

A different approach focused on investigating normal pancreatic parenchyma has been developed. Unlike pancreatic tumor, normal pancreatic tissue expresses receptor for bombesin. Hence, a bombesin peptide-coupled nanoparticle (BN-CLIO[Cy5.5]) can be used to image normal pancreas and hence, differentiate it from pancreatic tumors [100]. Similarly, in other studies, microbubbles (small gas-filled microspheres) have been used to image the peri-tumoral vasculature with the help of ultrasound. This technology can be potentially used to deliver anti-cancer therapies in future studies [101].

### ***Do we need tissue diagnosis before initiating treatment?***

A controversial subject is the need for pre-operative biopsy in patients with classic clinical and radiographic presentation of pancreatic adenocarcinoma. The advantage of performing biopsy is to confirm the diagnosis and minimize the risk of needless surgery for unsuspected benign disease. Disadvantages include the changes of false negative biopsy and risk of delaying definite and curative surgical resection in early pancreatic cancer. Another potential downside is the risk of rare iatrogenic complications, such as post-procedure pancreatitis or theoretical dissemination of tumor cells along the needle tract (and beyond) during CT guided biopsy. In light of these controversies, the decision to perform pre-operative biopsy rests on the discussion between the surgeon and the patient. Most centers in the US favor pre-operative biopsy as a routine. However, several experts, especially from non-US centers, favor proceeding to surgery directly (without pre-operative biopsy) in clearly resectable pancreatic head cancers[102], with an understanding that the presence of unsuspected benign diseases have been reported in 5%-11% of all resected tumors on final pathology results[103-105]. On the flip side, patients who definitely require tissue diagnosis include high risk surgical candidates, non-surgical candidates, patients due to undergo neoadjuvant or palliative chemotherapy. EUS/FNA is the ideal modality for tissue diagnosis in these patients.

Not all patients presenting with pancreatic masses have the classic presentation and supporting radiographic imaging for pancreatic cancer. Two important examples include chronic pancreatitis and autoimmune pancreatitis, where clinical presentation (lack of alarm symptoms) and imaging characteristics favor a non-malignant etiology. In these situations, a pre-operative biopsy is essential to rule out malignancy so that unnecessary surgery can be avoided.

## TREATMENT

A detailed discussion on all available treatment options is beyond the scope of this article. A brief overview of the treatment options with an emphasis on controversies and recent advancements will be discussed. Patients with pancreatic cancer should ideally be evaluated and treated in a high volume center in a multidisciplinary environment. The actual treatment algorithm depends upon the stage of disease (Tables 1-4) and is generally divided into four subgroups (resectable, borderline resectable, locally advanced and unresectable, and metastatic) (Table 5).

### **Resectable tumors**

Early curative resection of pancreatic cancer offers the best meaningful overall survival. However, only 15%-20% of pancreatic cancers are potentially resectable at presentation. Resectable tumors are the ones in which tumors have no contact with major surrounding arteries (such as celiac artery, superior mesenteric artery, or common hepatic artery) and surrounding veins (superior mesenteric vein or portal vein) (Table 5). Surgery of choice for tumors in the head of pancreas include Whipple surgery (pancreaticoduodenectomy) and distal pancreatectomy for tumors in the body and tail of pancreas. As *per* all major guidelines, these patients should undergo surgical resection if they are appropriate surgical candidates.

Pancreatic surgery carries a high morbidity and mortality but if done by experienced surgeons in high volume centers, the outcomes are superior[106,107]. Surgery also provides useful diagnostic and prognostic information[108]. Several factors such as tumor stage, status of surgical margins[17,109], lymph node status [110], tumor differentiation[111], pre and post- resection serum CA 19-9[109] and cigarette smoking[112,113] help predict overall prognosis. Five-year survival after pancreaticoduodenectomy is 10% in node positive disease[114] and 30% in node negative disease[115]. More importantly, about two thirds of patients undergoing surgical resection with curative intent will find positive lymph nodes, which correlates with a poor prognosis. Hence, this justification is used by some experts to support the use of neoadjuvant therapy upfront in all resectable tumors.

### **Is there a role of neoadjuvant therapy in clearly resectable tumors?**

In contrast to the traditional practice of early resection in resectable tumors, the use of upfront neo-adjuvant therapy in clearly “resectable” pancreatic cancers has increased recently[116]. Some studies have supported its use[105,117-122] and others have largely debunked the idea[123,124]. The proponents of this approach highlight the fact that many such patients may already have micro-metastasis at the time of diagnosis. By providing chemo-radiation upfront, the tumors can be restaged after treatment and surgery can be offered only to the group of patients who still have localized disease. This approach will help decrease the incidence of patients presenting with grossly visible metastasis soon after surgery. Moreover, this approach helps systemic chemotherapy to be started as soon as possible, in contrast to the delay in starting chemotherapy up to 4 wk after surgery (as is routinely advised by the Oncologists). The decision to start upfront neoadjuvant therapy should ideally be made in a multidisciplinary environment in the setting of a clinical trial. There is no consensus on the best therapy for this purpose. In most centers, neoadjuvant therapy is not yet a standard treatment modality in resectable tumors outside of the context of a clinical trial[125]. For most patients with good functional status, the preferred treatment is a multiagent modified FOLFIRINOX regimen (oxaliplatin plus irinotecan with leucovorin and short term infusional fluorouracil regimen), followed by chemoradiotherapy.

### **Is pre-operative biliary drainage necessary before surgical resection?**

Another controversial subject in the management of patients with potentially resectable tumors in the head of pancreas presenting with biliary obstruction revolves around the need to perform pre-operative biliary drainage. Several studies have been done to address this question with the results revealing benefit[126], no clear benefit [127-129] or harm with this approach[130-134]. Despite overwhelming data showing potential lack of benefit or even harm in routine preoperative biliary drainage in patients with malignant biliary obstruction, many surgeons in the US routinely request biliary drainage due to perceived better post-operative outcome with this approach. The decision to choose the modality for biliary drainage (percutaneous transhepatic *vs* endoscopic) rests on the availability of expertise at the respective institution, location of the obstruction *etc.* Both techniques have advantages and disadvantages and should

**Table 1 Tumor-node-metastasis staging of pancreatic adenocarcinoma [American Joint Committee on Cancer Tumor-Node-Metastasis Staging of Pancreatic Cancer (8<sup>th</sup> edition, 2017)]-T staging**

<b>T</b>	<b>Primary tumor</b>
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ. This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤ 2 cm in greatest dimension
T1a	Tumor ≤ 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm and < 1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor > 2 cm and ≤ 4 cm in greatest dimension
T3	Tumor > 4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

**Table 2 Tumor-node-metastasis staging of pancreatic adenocarcinoma [American Joint Committee on Cancer Tumor-Node-Metastasis Staging of Pancreatic Cancer (8<sup>th</sup> edition, 2017)]-N staging**

<b>N</b>	<b>Regional lymph nodes</b>
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

**Table 3 Tumor-node-metastasis staging of pancreatic adenocarcinoma [American Joint Committee on Cancer Tumor-Node-Metastasis Staging of Pancreatic Cancer (8<sup>th</sup> edition, 2017)]-M staging**

<b>M</b>	<b>Distant metastasis</b>
M0	No distant metastasis
M1	Distant metastasis

be used in the right clinical scenario after due consultation in a multidisciplinary environment[135]. Transhepatic biliary drainage is generally performed for more proximal intrahepatic biliary obstruction and endoscopic biliary drainage is performed for extrahepatic biliary obstruction. The type of stent used (plastic *vs* metal stent) depends upon the endoscopist and the surgeon’s preference. A permanent metal stent is more commonly used as it does not need to be replaced if the tumor is deemed unresectable at the time of surgery[136].

All patients who undergo resection of tumor (without neoadjuvant therapy) should undergo repeat staging of the disease with CT scan and tumor markers before starting adjuvant chemotherapy. Adjuvant chemotherapy should be started within 2 mo of the surgery and should be continued for six months. As in neoadjuvant therapy, for patients with good functional status, the preferred treatment is a multiagent modified FOLFIRINOX regimen (oxaliplatin plus irinotecan with leucovorin and short term infusional flurouracil regimen). For patients with poor functional status, gemcitabine alone or gemcitabine plus capecitabine are reasonable options (Table 6). Addition of radiation therapy in the adjuvant setting is somewhat controversial and is usually reserved in a subgroup of patients with excellent performance status[137].

**Borderline resectable and locally advanced unresectable disease**

Pancreatic tumors are considered borderline resectable if there is suspected solid tumor contact with major surrounding vasculature (but less than 180 degrees of

**Table 4 Tumor-node-metastasis staging of pancreatic adenocarcinoma [American Joint Committee on Cancer Tumor-Node-Metastasis Staging of Pancreatic Cancer (8<sup>th</sup> edition, 2017)]-tumor-node-metastasis staging**

Stages	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

**Table 5 Criteria defining resectability status of pancreatic adenocarcinoma[30]**

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact (CA, SMA, or CHA)	No tumor contact with the SMV or PV or $\leq 180^\circ$ contact without vein contour irregularity
Borderline resectable	Pancreatic head/uncinate process: Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation. Solid tumor contact with the SMA of $\leq 180^\circ$ ; Solid tumor contact with variant arterial anatomy (ex: Accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery). Pancreatic body/tail: Solid tumor contact with the CA of $\leq 180^\circ$ ; Solid tumor contact with the CA of $> 180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (controversial)	Solid tumor contact with the SMV or PV of $> 180^\circ$ , contact of $\leq 180^\circ$ with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. Solid tumor contact with the IVC
Locally advanced	Head/uncinate process: Solid tumor contact with SMA $> 180^\circ$ ; Solid tumor contact with the CA $> 180^\circ$ . Pancreatic body/tail: Solid tumor contact of $> 180^\circ$ with the SMA or CA; Solid tumor contact with the CA and aortic involvement	Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

CA: Celiac axis; SMA: Superior mesenteric artery; CHA: Common hepatic artery; SMV: Superior mesenteric vein; PV: Portal vein; IVC: Inferior vena cava.

**Table 6 Treatment protocols for pancreatic adenocarcinoma in adjuvant setting**

Drug	Dose and route	Administration	Toxicity
<b>Adjuvant gemcitabine (cycle length: 4 wk)[156]</b>			
Gemcitabine	1000 mg/m <sup>2</sup> IV	Weekly ( $\times 3$ wk) followed by one week of rest	Myelotoxicity; Hepatotoxicity; Pulmonary toxicity; Thrombotic microangiopathy
<b>Adjuvant gemcitabine plus capecitabine (GemCap; cycle length: 28 d)[157]</b>			
Gemcitabine	1000 mg/m <sup>2</sup> IV	Given on days 1, 8, and 15	Myelotoxicity; Nonhematologic toxicity (including hepatotoxicity); Pulmonary toxicity; Thrombotic microangiopathy
Capecitabine	830 mg/m <sup>2</sup> per dose by mouth	Given on days 1 through 21	
<b>Modified FOLFIRINOX (cycle length: 14 d)[158-162]</b>			
Oxaliplatin	85 mg/m <sup>2</sup> IV	Given on day 1	Myelotoxicity; Diarrhea; Mucositis or hand-foot syndrome; Pulmonary toxicity; Neurotoxicity; Cardiotoxicity
Leucovorin	400 mg/m <sup>2</sup> IV	Given on day 1	
Irinotecan	150 mg/m <sup>2</sup> IV	Given on day 1	
Fluorouracil	2400 mg/m <sup>2</sup> IV	Given on day 1	

vascular involvement) on pre-operative imaging. If an obvious direct vascular invasion of  $> 180$  degrees is noted such that a resection is not possible, then it is called locally advanced and unresectable disease (which accounts for approximately 40% of all pancreatic tumors) (Table 5).

There is no universal consensus on how to approach the treatment of these tumors. These patients are discussed in a multidisciplinary tumor board where appropriate treatment strategy is discussed in light of the patient's functional status, tumor biology (status of genetic mutations), pre-treatment imaging and many other factors.

A reasonable approach in patients with a borderline resectable disease is to attempt at downstaging with chemotherapy/chemoradiation followed by surgical exploration (if no metastatic disease is found on restaging)[137]. For patients with unresectable disease, enrollment in clinical trials using new treatment strategies should be encouraged. Prompt initiation of chemotherapy is warranted. Patients with homologous recombination repair (HRR) mutations and good performance status could benefit from aggressive medical therapy with FOLFIRINOX (short term fluorouracil, plus leucovorin, irinotecan, and oxaliplatin). A detailed discussion on the various treatment regimens and available clinical trials is beyond the scope of this article but a brief summary of the most common treatment regimens is summarized in Table 7.

### **Metastatic pancreatic cancer**

Prognosis of metastatic pancreatic cancer is poor with an expected 5-year mortality to be greater than 97%. Hence, it is important to discuss the patient's preference and goals of care before initiation of treatment. Early involvement of the palliative care team is beneficial. Genetic testing should be performed to determine the presence of HRR deficiency. Genes associated with HRR deficiency include *BRCA1/2*, *PALB2*, *ATM*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *FAM175A*, *FANCA*, *FANCC*, *NBN*, *RAD50*, *RAD51*, *RAD51C*, and *RTEL1*.

For metastatic disease in the setting of known HRR mutation, a platinum based chemotherapy regimen is preferred[138]. For patients with excellent functional status (ECOG PS 0 or 1) and serum bilirubin < 1.5x upper limit of normal, an aggressive medical therapy with FOLFIRINOX or modified FOLFIRINOX should be considered. Other alternatives included FOLFOX (leucovorin plus infusional fluorouracil plus oxaliplatin, if serum bilirubin is > 1.5), and a combination of gemcitabine plus cisplatin (Table 7).

After 16 wk of chemotherapy, maintenance treatment is considered based upon the results of genetic mutation analysis. For patients with certain genetic mutations such as germline *BRCA* mutation and *PALB2* mutation, maintenance therapy with poly(ADP-ribose) polymerase inhibitor Olaparib is initiated[138,139].

If no HRR mutation is detected in patients with good functional status and low serum bilirubin (< 1.5 × ULN), an aggressive regimen such as FOLFIRINOX should be considered. Other alternatives include modified FOLFIRINOX and gemcitabine plus nonparticle albumin-bound paclitaxel (nabpaclitaxel). However, for patients with higher bilirubin (> 1.5 × ULN), a gemcitabine-based regimen can prove to be toxic and should be avoided; instead, a FOLFOX based regimen should be considered in this setting) (Table 7).

For patients with suboptimal functional status (ECOG PS of 2), monotherapy with gemcitabine or gemcitabine plus capecitabine can be considered. Gemcitabine plus nabpaclitaxel can be toxic and should be reserved for highly selected patients with high tumor burden (Table 7).

For patients with very poor functional status or severe existing co-morbidities, systemic chemotherapy should be considered cautiously. Palliative care should be involved early on with an emphasis on the control of symptoms (such as severe pain).

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## **PALLIATION**

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Symptom palliation in patients with advanced pancreatic cancer is very important and is an integral part of the overall treatment plan[140]. The most common symptoms that require palliation include relief of obstructive jaundice (in tumors of the head of pancreas), duodenal obstruction (from tumor invasion) and severe debilitating pain. Other symptoms include risk of thromboembolism, anxiety/depression, anorexia and weight loss.

Palliative options in patients with malignant obstructive jaundice include biliary stenting and surgical biliary bypass. Randomized trials between the two approaches have shown no difference in survival; patients with stents have less procedure related morbidity and mortality but a higher rate of hospital readmissions from stent occlusion[141-143]. Since the advent of self-expandable metal biliary stents, however, stent occlusion has become less common compared to the traditional plastic biliary stents[143,144]. Biliary stenting can be performed endoscopically or percutaneously

**Table 7 Treatment protocols for locally advanced/metastatic pancreatic adenocarcinoma**

Drug	Dose and route	Administration	Toxicity
<b>Gemcitabine monotherapy (cycle length: 8 wk for first cycle, then 4 wk)[163-166]</b>			
Gemcitabine	1000 mg/m <sup>2</sup> IV	Weekly (× 7 wk) followed by one week of rest in the first cycle, then weekly (× 3 wk) followed by one week of rest in all subsequent cycles	Myelotoxicity; Hepatotoxicity; Pulmonary toxicity; Thrombotic microangiopathy
<b>Gemcitabine plus nanoparticle albumin-bound paclitaxel (nabpaclitaxel) (cycle length: 4 wk)[167,168]</b>			
Nabpaclitaxel	125 mg/m <sup>2</sup> IV	Given on days 1, 8, and 15	Myelotoxicity; Sepsis; Thrombotic microangiopathy; Peripheral neuropathy; Hepatotoxicity; Pulmonary toxicity
Gemcitabine	1000 mg/m <sup>2</sup> IV	Given on days 1, 8, and 15	
<b>Gemcitabine plus capecitabine (cycle length: 21 d)[157,169]</b>			
Gemcitabine	1000 mg/m <sup>2</sup> IV	Given on days 1 and 8	Myelotoxicity; Nonhematologic toxicity (including hepatotoxicity); Pulmonary toxicity; Thrombotic microangiopathy
Capecitabine	650 mg/m <sup>2</sup> per dose by mouth	Given on days 1 through 14	
<b>Gemcitabine plus cisplatin (cycle length: 21 d)[170]</b>			
Cisplatin	25 mg/m <sup>2</sup> IV daily	Given on days 1 and 8	Myelotoxicity; Thrombotic microangiopathy; Pulmonary toxicity; Hepatotoxicity; Neurotoxicity; Nephrotoxicity
Gemcitabine	1000 mg/m <sup>2</sup> IV daily	Given on days 1 and 8	
<b>FOLFIRINOX (fluorouracil plus leucovorin, irinotecan, and oxaliplatin) (cycle length: 14 d)[160,161]</b>			
Oxaliplatin	85 mg/m <sup>2</sup> IV	Given on day 1	Myelotoxicity; Diarrhea; Mucositis or hand-foot syndrome; Pulmonary toxicity; Neurotoxicity; Cardiotoxicity
Leucovorin	400 mg/m <sup>2</sup> IV	Given on day 1	
Irinotecan	180 mg/m <sup>2</sup> IV	Given on day 1	
Fluorouracil	400 mg/m <sup>2</sup> IV bolus	Given on day 1	
FU	2400 mg/m <sup>2</sup> IV	Given on day 1	
<b>Modified FOLFIRINOX (cycle length: 14 d)[158,159,161]</b>			
Oxaliplatin	85 mg/m <sup>2</sup> IV	Given on day 1	Myelotoxicity; Diarrhea; Mucositis or hand-foot syndrome; Pulmonary toxicity; Neurotoxicity; Cardiotoxicity
Leucovorin	400 mg/m <sup>2</sup> IV	Given on day 1	
Irinotecan	150 mg/m <sup>2</sup> IV	Given on day 1	
Fluorouracil	2400 mg/m <sup>2</sup> IV	Given on day 1	
<b>Modified FOLFOX6 (fluorouracil plus leucovorin and oxaliplatin) (cycle length: 14 d)[160,171,172]</b>			
Oxaliplatin	85 mg/m <sup>2</sup> IV	Given on day 1	Myelotoxicity; Neurotoxicity; Diarrhea; Cardiopulmonary toxicity
Leucovorin	400 mg/m <sup>2</sup> IV	Given on day 1	
Fluorouracil	400 mg/m <sup>2</sup> IV bolus	Given on day 1	
FU	2400 mg/m <sup>2</sup> IV	Given on day 1	
<b>Liposomal irinotecan and fluorouracil (cycle length: 14 d)[173]</b>			
Liposomal irinotecan	70 mg/m <sup>2</sup> IV	Given on day 1	Myelotoxicity; Diarrhea; Neurotoxicity; Cardiotoxicity
Leucovorin	400 mg/m <sup>2</sup> IV	Given on day 1	
Fluorouracil	2400 mg/m <sup>2</sup> IV	Given on day 1	
<b>Pembrolizumab monotherapy for microsatellite-unstable (mismatch repair-deficient) advanced cancer (cycle length: q3 weeks or q6 weeks)[174,175]</b>			
Pembrolizumab	200 mg IV	Given on day 1, every 3 wk	Pulmonary toxicity; Hepatotoxicity; Neurotoxicity;

OR

Dermatologic toxicity  
Cardiotoxicity

Pembrolizumab 400 mg IV Given on day 1, every 6 wk

(by Interventional Radiology). Endoscopic biliary stenting is preferable as it is associated with much lower complication rates and shorter hospital stays[145-147]. A permanent expandable metal biliary stent can be placed right after obtaining samples for tissue diagnosis (during EUS-FNA), allowing for one-step, efficient and effective care to these patients[148]. As there is no surgery involved, patients can be started on chemotherapy soon afterwards (without waiting for the post-op recovery as is seen in patients undergoing surgical bypass procedure). If endoscopic management is not feasible, external biliary drainage can be attempted. Percutaneous transhepatic biliary access (by Interventional Radiology) results in the placement of a percutaneous internal-external drain which can be replaced by percutaneous metal biliary stent placement in a few weeks[146]. In rare situations, surgical biliary bypass (such as hepaticojejunostomy, choledochojejunostomy or cholecystojejunostomy) may be needed.

Locally advanced pancreatic cancer can infiltrate the wall of duodenum resulting in malignant duodenal obstruction in approximately 15%-20% of patients[149]. This can be treated by surgical gastrojejunostomy or endoscopic enteral stent placement. Recent data on the utility of endoscopic stent placement has revealed good short-term efficacy, improved cost-effectiveness and shorter recovery time[150]. There are few studies comparing surgical bypass (gastrojejunostomy) to endoscopic stent placement in patients with malignant gastric outlet obstruction[151]. The decision on proceeding with one option vs. the other should be made in light of the patient's preference, performance status, disease stage, overall health condition and expected life expectancy. Overall, if the life expectancy is short (say 2-3 mo), an endoscopic stent is favored due to prompt relief of symptoms and short duration of recovery. If the expected life expectancy is longer, then surgical bypass is a more reasonable and durable approach due to better long-term results[151].

Cancer-related pain is a very common symptom in patients with advanced pancreatic cancer[152], resulting in decreased performance status and dismal quality of life. Opioid analgesics are most commonly used in managing severe pain associated with pancreatic cancer. Other adjunctive medications include gabapentin, pregabalin, nortriptyline, or duloxetine. In select situations, celiac plexus neurolysis (CPN) can be more effective for immediate and long-term pain relief[152,153]. CPN is preferred over radiation as the onset of action is quicker and long lasting[154,155]. In patients with pain associated with underlying depression and anxiety, antidepressant medications may be beneficial.

The risk of venous thromboembolism is 4-7 folds higher in pancreatic cancer as compared to other common adenocarcinomas. Patient education is key to recognize early signs of thromboembolism. Prophylaxis is recommended with low molecular weight heparin, low dose unfractionated heparin or fondaparinux in high-risk patients such as hospitalized patients with known pancreatic cancer. Lifelong treatment is generally required in patients who develop thromboembolism. Common recommended agents include low molecular weight heparin or a direct oral anticoagulant (*e.g.*, rivaroxaban, apixaban, edoxaban).

Poor appetite and weight loss in patients with advanced pancreatic cancer is common. Unfortunately, this correlates with disease activity and in many situations is a direct biological sequelae of tumor progression. Other factors such as severe depression and severe debilitating pain may contribute to these symptoms as well. Early referral to Nutritionist and/or dietician, dietary supplements and appetite stimulants (such as megestrol acetate) may help in these difficult situations. Patients who exhibit signs of pancreatic insufficiency (such as diarrhea and weight loss) may benefit from oral pancreatic enzyme replacement therapy.

## CONCLUSION

Despite recent advances in the diagnosis and treatment of pancreatic cancer, the survival of pancreatic cancer has not significantly improved. This poor prognosis is mainly due to the aggressive tumor biology of pancreatic adenocarcinoma and its potential for micro metastasis at an early stage of the disease. Early diagnosis and curative resection, when possible, correlates with improved survival but surgery in

itself carries a definite morbidity and mortality, even in specialized centers. Neoadjuvant therapy (instead of surgery upfront) in these patients is being offered in some centers but whether this approach consistently translates to better survival is not known. On the other hand, controversies such as the need for routine pre-operative biliary drainage and histological diagnosis before surgery have been addressed by good quality studies, but the results have not translated into clinical practice universally. Nevertheless, there is an overall consensus that while we continue to find the best treatment options, patients with pancreatic cancer should be managed in light of published guidelines at high volume centers in a multi-disciplinary setting.

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