

**HIGHLIGHT ARTICLE - Slide Show**

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## **Supportive and Palliative Care of Pancreatic Cancer**

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### **Summary**

Pancreatic cancer is one of the most lethal malignancies. An estimated 32,300 patients will die of pancreatic cancer in year 2006. It is the tenth most common malignancy in the United State. Despite recent advances in pathology, molecular basis and treatment, the overall survival rate remains 4% for all stages and races. Palliative care represents an important aspect of care in patient with pancreatic malignancy. Identifying and treating disease related symptomology are priorities. As a physician taking care of these patients it is essential to know these symptoms and treatment modalities. This review discusses symptom management and supportive care strategies. Common problems include pain, intestinal obstruction, biliary obstruction, pancreatic insufficiency, anorexia-cachexia and depression. Success is needed in managing these symptoms to palliate patients with advanced pancreatic cancer. Pancreatic cancer is a model illness to learn the palliative and supportive management in cancer patient. It is important for oncologists to recognize the importance of control measures and supportive measures that can minimize the symptoms of advanced disease and side effects of cancer treatment.

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**Supportive and Palliative Care of  
Pancreatic Cancer**

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**Clinical Features**

- Pain: 80% (splanchnic plexus; retroperitoneum)
- Jaundice: 47%
- Weight loss: 60%
- New onset diabetes mellitus
- Paraneoplastic syndromes
- Courvoisier's sign
- Hepatomegaly

The presenting symptoms of pancreatic cancer can include pain, unexplained weight loss, nausea, vomiting, steatorrhea, dyspepsia, depression and jaundice. There are no well known warning signs of pancreatic cancer. However, new onset diabetes in an old patient has been associated with pancreatic cancer. Although painless jaundice is often thought as

the typical presentation of pancreatic cancer, most of the patient have mild to moderate abdominal pain. Back pain usually suggests involvement of retroperitoneal nerves. Jaundice usually develops in patient with tumor in the head of pancreas, on the other hand, tumor in the tail of pancreas do not present with jaundice. Paraneoplastic syndromes may manifest as depression or thrombophlebitis. On physical examination, about 50% of patients have jaundice. Occasionally they may have palpable gall bladder (Courvoisier's sign). Hepatomegaly may be present due to metastatic liver disease.

**Supportive and Palliative Care of Pancreatic Cancer**

- Pain Management
- Intestinal Obstruction
- Biliary Obstruction
- Depression
- Fatigue
- Pancreatic Insufficiency
- Cachexia

Prompt management must include efforts to palliate patients with advanced pancreatic cancer. Common problems include biliary obstruction, depression, pain, intestinal obstruction, and fatigue.

**Pain – It Not Just Pain !**

- People frequently equate suffering with intolerable pain
- Joint Council on Accreditation of Health Care Organization's introduction of pain as the fifth vital sign

**Presentation**

- Pain syndromes associated with pancreatic cancer arise due to involvement of critical structures surrounding pancreas

**Prevalence**

- 75-80% of patients present with pain at initial presentation
- 44% of patients admitted to palliative care setting has severe pain [1]
- Pain is linked with depression and anxiety and it underlines the importance of treating pain

[1] Brescia FJ, et al. J Clin Oncol 1992;10:149-55.

Pain is the most treatable cancer complaint. In patients with pancreatic cancer, it can arise due to involvement of the critical structures such as: the duodenum, liver, stomach, jejunum and transverse colon. Patients with obstruction of the intestines would develop

colicky pain with abdominal distention. Involvement of the liver produce right upper quadrant pain and sometimes referred pain to the right shoulder or neck. Pain is usually worrisome for both patient and family. Some people would equate the suffering with intolerable pain. [1]

**Pain**

- Half of the respondents in a state wide survey believed physicians cannot make a difference. 18% reported that they might be reluctant to seek medical attention for cancer treatment [2]

**General rules [3]**

- Pain control starts with routine screening and assessment
- The principle with assessment scale is using the same tool consistently for the same patient for serial assessment
- Pain medications should be administered on a scheduled basis
- *prn*<sup>a</sup> or rescue doses should be available for breakthrough pain or pain not controlled by the standing regimen
- Rescue dose should be calculated at approximately 10-15% of the 24 hour baseline dose
- All patients on opioids should be started on a bowel regimen

<sup>a</sup>prn: pro re nata (as needed)

[2] Levin DN, et al. Cancer 1985; 56:2337-9.  
[3] Morrison LJ, Morrison RS. Med Clin North Am 2006; 90:983-1004.

These are general rules in managing patient with cancer pain. Pain is subjective sensation and cannot be objectively validated. In order to assess the pain, physicians have to rely on self reporting from the patients. Multiple tools are available to assess the severity of the pain. However the important principle is to use the same assessment scale consistently for serial evaluation. Fortunately when pain is recognized, in more than 80% of patient it can be brought under control with basic management. [2, 3]

**Pain Management with Systemic Analgesic Therapy [4]**

**The WHO analgesic ladder is useful in achieving acceptable pain relief**

- Treat **mild pain** with *acetaminophen, NSAIDs* and less commonly *aspirin*
- Treat **moderate pain** with *weak opioids* and combination products such as *hydrocodone-acetaminophen, oxycodone-aspirin* and *tramadol*
- Treat **severe pain** with *morphine, hydromorphone, fentanyl* and *oxycodone*

[4] McDonnell FJ, et al. Curr Oncol Rep 2000; 2:351-7.

In addition to above medications steroids, anticonvulsants, antidepressants and bisphosphonates can be useful in managing pain. [4]



**Key Issues in Pain Management with Systemic Analgesic Therapy**

- It is important to realize that medications containing *acetaminophen* and *NSAID* - i.e combination products - have ceiling doses
- It is important that *acetaminophen* containing medications should be used with caution in patients with liver metastasis
- *NSAID* use may be limited due to deleterious side effects, which most commonly occurs on the gastrointestinal tract
- *Propoxyphene* and *meperidine* should be avoided especially in elderly population

NSAIDs are the first line agents for managing mild pain. Their use may be limited due to potential deleterious side effects. Patients should be evaluated for risk factors to develop serious side effects. Patients who are above 60 years, on concurrent anticoagulation, steroid therapy, or with the past history of gastrointestinal bleeding are more prone to develop serious gastrointestinal side effects. Acetaminophen should be administered in dose less than 4 g/day. However physicians need to be more cautious in patients with alcoholic liver disease or hepatic metastasis. Propoxyphene and meperidine should be used with caution in elderly as its metabolites may build up to cause neurotoxicity and lower the seizure threshold.

**Key Issues in Management**

- It is important to routinely assess for constipation especially while on opioids
- Most patients respond to stool softener plus escalating dose of stimulant
- Adequate hydration, physical activity and regular toileting can be useful
- If dose escalation fails , use agents from different class
- Some of the commonly used agents are

<b>Stool softeners</b>	Docusate sodium, calcium docusate
<b>Stimulant laxatives</b>	Prune juice, senna, bisacodyl
<b>Osmotic laxatives</b>	Lactulose, propylene glycol, milk of magnesia, magnesium citrate
<b>Miscellaneous</b>	Large volume tap water enema, high-colonic enemas, or manual disimpaction

Sedation and nausea are common opioids side effect but usually patients develop tolerance to them. Constipation can be fairly common problem in patients receiving opioids for pain control. Patients underreport constipation and life threatening complications of fecal impaction and perforation can develop quickly if bowel movements are not

maintained. Constipation is a side effect of opioids to which very few people show tolerance. For this reason, all patients on opioids need to receive a prophylactic bowel regimen of a stool softener and stimulant laxative, unless contraindicated.

**Commonly Used Laxative Regimens and Their Doses**

Medication	Dose	Comments
<b>Docusate</b>	Oral: 50-500 mg/day in 4 divided doses. Rectal: 50-100 mg. Add docusate to enema fluid and give as a retention or flushing enema	Docusate is available in different salts. It is ineffective alone. Need to take for 1-3 days to soften stools
<b>Senna</b>	Oral: usual dose 15 mg once daily, may use up to 70-100 mg/day in 2 divided doses. Dose varies between 2 tablets daily to 4 tablets twice daily	Effect occur in 6-24 h May use in combination pills with docusate
<b>Bisacodyl</b>	Oral: 5-15 mg/day, Rectal: suppository 10 mg as single dose	Effect occur in 6-10 h
<b>Lactulose</b>	Oral: 10-20 g/day, may increase to 40 g/day in divided doses	
<b>Milk of magnesia</b>	Liquid: 30-60 mL/day in divided doses Tablets: 6-8 tablets/day	Use with caution in patients with impaired renal function
<b>Magnesium citrate</b>	Liquid 120-300 mL/day	Use with caution in patients with impaired renal function

**Key Issues in Pain Management with Systemic Analgesic Therapy**

- Withdrawal to opioids can develop if the dose is reduced too fast or abruptly
- Usually withdrawal can be avoided by gradual tapering over days, usually 50% dose decrease per day or slower

**Pain Management**

**Common reasons for failure**

- Error in dosing
- Failing to start scheduled dosing
- Failing to escalate the baseline and breakthrough dose
- Failure to address side-effects
- Familiar with the issues related to tolerance, dependence, addiction and "pseudoaddiction"
- Familiar with use of alternative opioids and adjuvant analgesics such as antidepressant, anticonvulsants, biphosphanates and corticosteroids

It is important to know the common reasons for inadequate pain control. Pain control is better with scheduled or around the clock dosing. Tolerance and dependence are pharmacological properties of pain

medications. Pseudoaddiction refers to iatrogenic phenomenon resulting from poorly controlled pain. Patient exhibit features like frequent clock watching and repeated requests for pain medication. The behavior usually disappears after the pain is adequately controlled.

#### Pain Management: Interventional Techniques

- **Neurolytic celiac plexus blockage** can be beneficial interventional technique
- **Principle:** the celiac plexus is primarily a sympathetic central nervous system structure mediating nociceptive transmission from upper abdominal viscera
- **Effective palliation** has been shown to improve quality of life and, has been suggested to improve survival [5, 6]
- **Neurolysis** achieved by percutaneously injecting phenol or alcohol in to celiac plexus can be helpful for 3-6 months
- **Alternate nociceptive pathway** exists which requires continued use of opioids
- **Useful** in patients who develop intolerable side effects, or whose pain is inadequately controlled with the non interventional approaches
- **Complications** are rare (gangrene of bowel, pneumothorax, paraplegia)

[5] Staats PS, et al. Pain Med 2001; 2:28-34.  
[6] Lillemoe KD, et al. Ann Surg 1993; 217:447-55.

We have interventional pain management techniques. It is important to realize that they are not the last resort, but a valuable tool in the optimal care of cancer patients. One major interventional modality for pain control is anesthetic block of celiac plexus. The effect is unfortunately not permanent and severe pain can return after a variable interval (3-6 months). The neurological complications associated with neurolytic celiac block engenders the greatest concern. Orthostatic hypotension can happen in 1-3% of patients and usually lasts up to 5 days. Diarrhea (38%) may result from sympathetic blockage to the GI tract. Abdominal aortic dissection and retroperitoneal hemorrhage are rare complications. [5, 6]

#### Laparoscopic Celiac Plexus Block for Pain Relief in Patients with Unresectable Pancreatic Cancer

- **Neurolytic celiac plexus block** is usually performed using a posterior percutaneous approach aided by CT scan
- **Laparoscopic neurolytic celiac axis block** has been suggested to be performed at the time of staging laparoscopy
- **Strong et al.** reported 9 patients who underwent the procedure without any substantial adverse reaction [7]
- **Efficacy** of this technique is unknown

[7] Strong VE, et al. J Am Coll Surg 2006; 203:129-31.

Neurolytic celiac plexus block is usually performed using a posterior percutaneous approach aided by CT scan. On the other hand, laparoscopic neurolytic celiac axis block can be performed at the time of staging laparoscopy. [7]

#### Pain Management: Interventional Approaches

- **Intraspinal drug delivery** can be highly effective adjunctive interventional technique
- **Intraspinal technique** would achieve analgesia without the systemic side effects [8]
- **Equivalent analgesic dose** for intrathecal morphine is 1% of the systemic dose
- **Useful** in selected patients with intolerable cancer pain
- **Smith et al.** reported the value of implantable drug delivery by showing survival benefit in patients with refractory cancer pain [9]
- **Complications** associated with intrathecal administration is very low. (infection, mechanical malfunction, catheter obstruction, CSF leakage and hematoma)

[8] Seamans DP, et al. J Clin Oncol 2000; 18:1598-600.  
[9] Smith TJ, et al. J Clin Oncol 2002; 20:4040-9.

Intraspinal drug delivery via intrathecal or epidural route can be useful interventional technique. It allows to decrease the systemic side effects of oral opioids therapy. The economic issue can be an additional consideration favoring its use over the systemic analgesic therapy. However, intraspinal drug delivery cannot be provided without a proper team. [8, 9]

#### Pain Management: Chemotherapy and Radiation

- **Chemotherapy** with gemcitabine can achieve pain control. About 24% of patient treated with gemcitabine experienced improved pain and/or fatigue [10]
- **Radiation therapy with chemotherapy** can be used as palliative modality
- **Capecitabine and concurrent radiation therapy** appears safe and well tolerated without unexpected toxicities [11]
- **No randomized controlled trials** to evaluate its effectiveness as compared to other interventional approaches

[10] Burris HA 3rd, et al. J Clin Oncol 1997; 15:2403-13.  
[11] Saif MW, et al. J Clin Oncol 2005; 23:8679-87.

Chemotherapy can be helpful in controlling pain and fatigue. External beam radiation with chemotherapy can be used. However, the pain control may take several weeks. Study done by Saif et al. demonstrated the safety of using radiotherapy with capecitabine for locally advanced pancreatic cancer. [10, 11]



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**Intestinal Obstruction**

- Usually preterminal event
- **Incidence** of duodenal obstruction is 7-50%
- A thorough history and physical examination should be performed to differentiate from other complications such as opioids related nausea, constipation, and ileus [12]
- **Supportive management** with nasogastric suctioning and fluid resuscitation has short term benefit
- **Medical management** is usually difficult and success is dependent upon the level and degree of obstruction
  - Anticholinergic    • Dexamethasone
  - Anti-emetic        • Haloperidol
  - Opioids             • Octreotide

Can be helpful to some extent with nausea, pain and increased secretions

[12] Brescia FJ. Cancer Control 2004; 11:39-45.

Intestinal obstruction is a late complication of advanced pancreatic cancer. It is important to evaluate for other causes which can present in similar way. Nasogastric suctioning can decompress the bowel and relieve some of the abdominal distention and pain. Pharmacological interventions can be helpful to some with intestinal obstruction, nausea and increased intestinal secretions. [12]

**Intestinal Obstruction [13, 14, 15]**

- **Aggressive nutritional management with TPN**
  - Benefit unknown
  - For selected patients whose survival and quality of life might be enhanced by chemotherapy
- **Surgical intervention** is usually considered futile
  - Gastrojejunostomy is common palliative surgical procedure for gastric outlet obstruction
- **Radiation and chemotherapy** offer little help
- **Expandable metal stents** can be helpful in selected patients
  - Approximately 90 % of patient with gastroduodenal stents improve clinically
  - Complications include perforation, bleeding, stent malposition, stent migration and occlusion by tumor overgrowth
  - Safety unknown in patients, who have received or currently receiving chemoradiation

[13] Jeumink SM, et al. Ned Tijdschr Geneesk 2006; 150:2270-2.

[14] Baron TH. N Engl J Med 2001; 344:1681-7.

[15] Davis MP, Nouneh C. Curr Oncol Rep 2000; 2:343-50.

No data are available to support the use of aggressive parenteral nutrition in patient with advanced terminal disease. The advantage of

surgical intervention such as gastrojejunostomy is long term efficacy. A disadvantage is prolonged postoperative course. Endoscopic stent placement can be helpful in some non-surgical patients with gastroduodenal obstruction. Patients may resume oral intake almost immediately after the successful stent placement. However, some patients may not improve after the stent placement. They may have obstruction at multiple level, or functional obstruction due to gastrointestinal dysmotility. Around 20% of patients require re-intervention because of recurrent symptoms. [13, 14, 15]

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**Biliary Obstruction**

- Common initial presentation of patients with tumor in the head of pancreas
- May occur later in the course due to obstruction caused by regrowth of resected tumor, enlarged lymph node, or biliary stent occlusion
- **Presentation:** obstructive jaundice usually presents with icterus of skin and mucous membranes, pruritus, alcoholic stools, malabsorption, weight loss and dark urine
- **Treatment:** relief of biliary obstruction can reduce symptoms, improve quality of life and has been associated with longer survival [16]
- **Biliary decompression**
  - Surgical (cholecystojejunostomy, choledochojejunostomy, or hepaticojejunostomy)
  - Biliary stenting

[16] Sarr MG, Cameron JL. Surgery 1982; 91:123-33.

Around 90% of patients will have jaundice during some stage of their illness. The optimal management of these patients will vary depending upon their age, life expectancy, performance status, potential resectability of the tumor and physician's expertise. Surgical decompression may be the best option for patient undergoing laparotomy for potential resection. Biliary bypass has been associated with improved survival and

higher quality of life as compared to diagnostic laparotomy. [16]

#### Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer

- Recently a randomized trial was done in Brazil which aimed at evaluating quality of life and cost of care in patients undergoing endoscopic biliary drainage versus surgical drainage [17]
  - Patients in endoscopic group arm underwent biliary drainage with the insertion of metal stent.
  - Patient in surgical procedure underwent choledochojejunostomy and gastrojejunostomy
- Endoscopic procedures were much cheaper than the surgical procedure, when compared in terms of cost of procedure, cost of care during initial 30 days and overall total cost of care.
- There was no difference in complication rate, readmissions for complications and duration of survival
- Similar result was seen by Raikar *et al.* in a study conducted between 1990 and 1992 [18]

[17] Artifon EL, et al. Am J Gastroenterol 2006; 101:2031-7.  
[18] Raikar GV, et al. Ann Surg Oncol 1996; 3:470-5.

It is commonly believed that surgical drainage are cheaper palliative procedure. In a prospective, randomized controlled trial conducted in a tertiary referral center in Brazil, quality of life and cost of care were evaluated [17]. Patients with biliary obstruction due to metastatic pancreatic cancer and liver metastasis (without gastric outlet obstruction) were included in the study. Endoscopic biliary drainage with the insertion of a metal stent into the bile duct was compared with the surgical drainage procedure (choledochojejunostomy and gastrojejunostomy). Both surgical and endoscopic drainage procedures were successful, without any mortality in the first 30 days. The cost of biliary drainage procedure, the cost of care during the first 30 days after drainage, and the overall total cost of care were lower in the endoscopy group compared with the surgical group. In addition, the quality of life scores were better in the endoscopy group at 30 days (P=0.042) and 60 days (P=0.05). There was no difference between the two groups in complication rate, readmissions for complications, and duration of survival. Similar result was seen by Raikar *et al.* in a study conducted between 1990 and 1992 [18].

#### Stents

- Stents can be placed during ERCP or PTC
- **Preparation** prior to ERCP/PTC
  - Refrain from eating drinking for at least 6 hrs prior to the procedure
  - Make sure patient is not allergic to iodine
- **Aftercare**
  - Monitor for signs and symptoms of complications related to procedure
  - After PTC, measures to reduce bleeding from injection site

Biliary stenting can be done by ERCP (endoscopic retrograde cholangiopancreatography) or PTC (percutaneous transhepatic cholangiopancreatography). ERCP is an imaging technique used to diagnose diseases of hepatic and pancreaticobiliary origin. It usually involves inserting an endoscope into patient's mouth. After visualizing the biliary duct orifice, a cannula is inserted, which is then used to inject dye into biliary system. X-rays are then taken to visualize any pathology of biliary system. Special instruments are used to place stents. PTC is similar to ERCP, however it is usually reserved for patients who cannot undergo ERCP. It involves inserting a needle thru the skin and reaching liver. Dye is injected into the biliary system. Stents can also be placed after visualizing level of obstruction. Prior to the procedure, patients are usually made *npo* (nothing by mouth) at least 6 hours prior to the procedure. Antibiotics will be started prior to the surgery and continued for several days afterwards. After the ERCP, patient usually stays in the hospital or outpatient facility until the effects of the sedative wear off and to ensure no complications occur. After PTC, the patient is instructed to lie on his or her right side for at least 6 hours to reduce the risk of bleeding. Patients should be frequently assessed to assess that the stent is functioning properly.



Complications of Biliary Stenting	
Endoscopic retrograde cholangiopancreatography	Percutaneous transhepatic cholangiography
Excessive Bleeding	Bleeding
Infection	Infection of the injection site
Pancreatitis	Sepsis
Cholangitis	Leakage of the dye into abdomen
Cholecystitis	
Injury to the intestines	

The rate of serious complications with ERCP is approximately 11%, and 5-10% with PTC. Complications related to stent are not mentioned over here.

Biliary Obstruction
<ul style="list-style-type: none"> <li>➤ Most patients are best palliated with stent placement</li> <li>➤ Endoscopic stent placement is preferred over percutaneous approach [19]</li> <li>➤ Expandable or Teflon® stent versus a plastic stent - practical decision [20]</li> <li>➤ Prophylactic bypass procedures are not useful</li> <li>➤ Recent data shows that newly designed plastic stents (Tannenbaum) has better duration of patency than the polyethylene stent</li> </ul>

[19] Speer AG, et al. Lancet 1987; 2:57-62.  
 [20] Haringsma J, Huijbregtse K. Endoscopy 1998; 30:718-20.

Most patients are best palliated by stent placement (endoscopic or percutaneous) due to its lower complication rate and lower cost. Endoscopic stenting has higher success rate and lower 30 day mortality rate. Plastic stents have more complications, but they are removable. So they are more viable option in patients who are getting neoadjuvant chemoradiation therapy. On the other hand, metallic stents are more durable and are recommended in patients with metastatic or unresectable cancer. [19, 20]

Tannenbaum Stents
<ul style="list-style-type: none"> <li>➤ In a study done by Katsinelos et al. [21] Tannenbaum stent were found to be cost effective as compared to metal stent in patients with inoperable malignant distal common bile duct strictures</li> <li>➤ The median first stent patency was much longer in the metal group (255 vs. 123.5; P=0.002). However, the Tannenbaum stent are cheaper (17,700 vs. 30,100 euros)</li> <li>➤ Tannenbaum stents can be a reasonable option for patients with liver metastasis and expected short survival time</li> </ul>

[21] Katsinelos P, et al. Surg Endosc 2006; 20:1587-93.

At the time of diagnosis more than 80% of patients with malignant obstructive jaundice cannot undergo operative resection. Endoscopic intervention with stenting is an important palliative technique. However stent clogging is the major limitation. Metal stents have better patency than the plastic stent, however they are more expensive. In a study done by Katsinelos et al. Tannenbaum stent were found to be cost effective as compared to metal stents [21].

Characteristics of Stents (I)		
Type	Make up	Factors to consider in deciding the type of stent
Plastic	Nylon	<ul style="list-style-type: none"> <li>• Less expensive as compared to metal stents. Reasonable choice in patient with advanced disease and reduced survival (3-6 months)</li> <li>• Tannenbaum stents has better patency rate as compared to polyethylene stents</li> <li>• May be used to assess the patency of occluded metallic stent</li> </ul>
	Polyethylene <sup>a</sup>	
	Polyurethane	
	Teflon	
	Double layer Tannenbaum	
Metal	Nitinol	<ul style="list-style-type: none"> <li>• Patients with longer expected survival &gt;6 months should have SES<sup>b</sup></li> <li>• Metal stents have higher initial cost. There is no difference in cost per patient in those surviving less than 6 months. It has higher cost per patient in patients surviving less than 3 months</li> <li>• Removal of metallic stent is virtually impossible</li> <li>• Usually the stent of choice to open occluded plastic stents</li> <li>• In patients with several comorbidities where it is not feasible to have second ERCP</li> <li>• Open mesh design of metallic stent in patients with biliary obstruction allows continued patency of contralateral ducts</li> </ul>
	Elgiloy (Membrane-coated metal stents are also used)	

<sup>a</sup> Polyethylene stents are the most common type of plastic stents  
<sup>b</sup> SES: self expandable stents

Characteristics of Stents (II)			
Type	Make up	Life time [22]	Complications <sup>b</sup>
Plastic	Nylon	-	<ul style="list-style-type: none"> <li>• Stent occlusion (increased as compared to metal stents)</li> <li>• Stent migration</li> <li>• Stent fracture (rare)</li> </ul>
	Polyethylene <sup>a</sup>	75.5 -142 days	
	Polyurethane	-	
	Teflon	83-181 days	
	Double layer Tannenbaum	123.5 days Risk of occlusion increases progressively after 3 months	
Metal	Nitinol	111-273 days	<ul style="list-style-type: none"> <li>• Stent occlusion</li> <li>• Stent migration</li> <li>• Stent fracture</li> </ul>
	Elgiloy (Membrane-coated metal stents are also used)		

<sup>a</sup> Polyethylene stents are the most common type of plastic stents  
<sup>b</sup> Complications related to ERCP have not been listed here

[22] Moss AC, et al. Cochrane Database Syst Rev 2006; 2:CD004200.

Endoscopic biliary drainage using the stents are effective way to palliate the patients with biliary obstruction. Plastic stents in sizes ranging from 7F to 11F have been used for this purpose. Increased diameter of the plastic stents are associated with lower stent occlusion. However, the size of plastic stent that can be easily deployed is limited by the size of endoscope. Self expandable metal stents, as the name suggests, allow a larger size of metal stent to be placed. Self expandable metal stents are associated with significantly longer patency. However, their higher initial cost is important factor to



consider in patients with shorter survival. The second important factor is that metal stents cannot be removed. So they are not useful in patients with potentially resectable tumors. Metal stents are also placed to open the occluded plastic stents. In patients with several co-morbidities where ERCP can be difficult, it is preferred to placed the metal stents due to their longer patency. Biliary stents coated with the chemotherapy agent such as carboplatin has been used in patients with cholangiocarcinoma. Antibiotic trials to prevent stent blockage has yielded mixed results. [22]

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**Depression**

**Prevalence**

- Depression is more common in patients with pancreatic cancer, when compared with patients with other intra abdominal malignancy
- In a study done by Fras *et al.*, 139 patients with possible colon and pancreatic cancer were evaluated. Prior to surgery the prevalence of depressive symptoms was 76% (pancreatic cancer) versus 17% (colon cancer) [23]
- Joffe *et al.* study showed that half of the patient with pancreatic cancer had depressive symptoms compared with none with gastric cancer [24]
- Kelsen *et al.* evaluated for depression and pain in patients with newly diagnosed pancreatic cancer [25]

[23] Fras I, et al. Am J Psychiatry 1967; 123:1553-62.  
 [24] Joffe RT, et al. Gen Hosp Psychiatry 1986; 8:241-5.  
 [25] Kelsen DP, et al. J Clin Oncol 1995; 13:748-55.

Depression has been demonstrated in 47-71% of patients with pancreatic cancer. The studies mentioned have shown increased prevalence of depression in this disease [23, 24]. The study done by Kelsen *et al.* had interesting findings [25]. However, they did not evaluate the patients receiving chemotherapy who are more likely to be depressed.

**Depression**

- 130 patients with pancreatic cancer were evaluated. 83 prior to surgical procedure and 47 before chemotherapy
- 29% of patients complained of moderate to severe pain. There was statistically significant difference in patients who complained of pain prior to chemotherapy as compared to patients before surgery
- 38% patients had high levels of depression
- There was significant correlation between increasing pain and depression and between pain and depressive symptoms and impaired quality of life
- A study done by Angelino *et al.* [26] suggests that patients with a prior history of depression has worse survival than would be expected on the basis of cancer diagnosis alone
- **Treatment** with brief psychotherapy and cognitive therapy is beneficial

[26] Angelino AF, Treisman GJ. Support Care Cancer 2001; 9:344-9.

Management of depression depends upon attention to adequate pain control, use of antidepressants and psychological support. [26]

**Commonly Used Antidepressants**

Antidepressants	Dose (mg; starting and usual dose)	Adverse reactions
Amitriptyline	25-50 , 100-300	Drowsiness, drymouth, constipation, confusion, sexual dysfunction, urinary retention, seizure
Nortriptyline	25 , 50-200	Same as above
Citalopram	20 , 20-60	Drowsiness, insomnia, headache, nausea, vomiting, diaphoresis, dry mouth
Escitalopram	10 , 10-20	Headache, somnolence, insomnia, nausea, ejaculation disorder
Fluoxetine	20 , 20-40	Nausea, vomiting, diarrhea, insomnia, sexual dysfunction, nervousness
Fluvoxamine	50 , 50-300	Headache, somnolence, insomnia, nervousness, xerostomia, nausea
Paroxetine	20 , 20-40	Nausea, vomiting, diarrhea, insomnia, sexual dysfunction, nervousness

Continues .....

..... continued.

Antidepressants	Dose (mg; starting and usual dose)	Adverse reactions
Sertraline	50 , 50-100	Nausea, vomiting, diarrhea, insomnia, sexual dysfunction, nervousness
Bupropion	150 , 300-450	Tachycardia, headaches, insomnia, weight loss, seizures, dizziness
Venlafaxine	37.5 , 75-300	Weakness, diaphoresis, nervousness, xerostomia, anorexia, nausea
Duloxetine	30 , 60-120	Somnolence, dizziness, headache, nausea, xerostomia, diarrhea
Trazadone	50 , 75-300	Sedation, dizziness, priapism, blurred vision, nausea, xerostomia
Mirtazapine	15 , 15-45	Somnolence, hypercholesterolemia, increased appetite, weight gain, constipation
Methylphenidate	2.5-5 , 10-20	Cardiac decompensation in elderly patients. Confusion, restlessness, dizziness, nightmares, insomnia, palpitations, tremors and arrhythmias

Most commonly used antidepressants are listed with the doses and their common adverse reaction. In general, it is best to start the antidepressants at a low dose and titrate up as the patient tolerates. This approach will help in minimizing side effects and aids in compliance.



**Key Points in Pharmacotherapy**

- The selection of antidepressant depends upon:
  - Life expectancy
  - Current medical problems
  - Side effect profile
- All antidepressants are similar in terms of efficacy
- The use of tricyclic antidepressants can be problematic if there is hepatic dysfunction (*nortriptyline* is preferred because of therapeutic window that allows drug level monitoring)
- Psychostimulants can be used in patients with short expected survival
- Selective serotonin reuptake inhibitor (SSRI) are most widely prescribed medications due to their efficacy and side effect profile
- *Mirtazapine* has anti-emetic and analgesic properties

The clinical trials have shown that all the antidepressants are approximately equal in terms of the efficacy. The choice of the antidepressants is dependent on the current medical problems, their side effect profile and life expectancy of the patient. It is important to identify the side effect profile and use it to work for patient benefit. Tricyclic antidepressants cause weight gain, sedation, constipation and urinary retention. So these agents might help someone who is having diarrhea, insomnia and weight loss. Once they are stabilized on an antidepressant, it is important to identify and treat the side effects still bothering the patient. Tricyclic antidepressants have analgesic properties and potentiates the analgesic effects of the opioids. Usually cancer patients with depression are sensitive to tricyclic antidepressants as compared patients with depression alone. SSRI are usually well tolerated, they have lesser side effects as compared to tricyclic antidepressants. Trazadone has sedating properties and is useful adjunct to patients who have annoying insomnia on SSRI. Psychostimulants such as methylphenidate, dextroamphetamine, mofadanil and pemoline can be useful to counteract fatigue, appetite and energy. Pemoline can cause hepatocellular injury and should be used with caution in patient with liver metastasis.

**Supportive and Palliative Care of Pancreatic Cancer**

- Pain Management
- Intestinal Obstruction
- Biliary Obstruction
- Depression
- **Fatigue**
- Pancreatic Insufficiency
- Cachexia

**Fatigue**

- Most common symptom in patients with cancer
  - 90% of patient's relative reported observing fatigue and oncologists describe 76% of their patients with fatigue
  - Fatigue can result from factors related to cancer and its treatment [27]
    - Pain
    - Depression and stress
    - Anemia
    - Opioids use
    - Insomnia
    - Dehydration
    - Cachexia
- Treatment of fatigue should aim in treating these factors

[27] Simon AM, Zittoun R. Curr Opin Oncol 1999; 11:244-9.

Cancer related fatigue is a subjective experience of tiredness that can influence the patient's ability to continue with the treatment and eventually can decrease the chance of antitumor effect of chemotherapy. It is important to recognize the several contributing factors outline above in each patient. Treatment is usually difficult and its important to treat the contributing factors. [27]

**Fatigue**

- Cancer treatments such as chemotherapy, radiation therapy, surgery or biological response modifier often induces fatigue [28]
- It may not only be the side effect during therapy but may also be a long term side effect of cancer treatment
- Screen for fatigue at every office visit
- **Management**
- **Patient education** regarding self management of fatigue
- Exercise and activity enhancement

[28] El Kamar FG, et al. Oncologist 2003; 8:18-34.

Causes of cancer related fatigue are diverse and are partially explained. Fatigue has been associated with chemotherapy. It has been found that fatigue is usually intense in first few days after chemotherapy. It usually abates over the next few days. Sometimes it can last for prolonged period after the completion of chemotherapy. Cancer related fatigue is a common problem and it should be routinely screening during and after cancer treatment. Patients should be educated about fatigue as a possible side effect of cancer treatment. Some patients can interpret it as a sign of tumor progression, education regarding it can help preventing anxiety. Self management means

that patient can prioritize their activities, so that fatigue does not prevent them from performing essential activities. Exercise and activity enhancement has been shown consistently to help in fatigue. It increases the functional capacity so that they can perform their activities with reduced effort. [28]

#### Management of Cancer Related Fatigue [29]

##### ➤ Pharmacological therapy

- Psychostimulants such as methylphenidate, and pemoline
- Erythropoietin for treating anemia

##### ➤ Non pharmacological therapy

- Psychosocial intervention
- Nutritional therapy

[29] Stasi R, et al. Cancer 2003; 98:1786-801.

Pharmacological therapy can be helpful in certain subsets of patients. Erythropoietin can improve hematocrit and increase the energy level in patients with anemia. Psychostimulants can reduce fatigue and depression in patients with malignancy. The side effects of methylphenidate and pemoline have been discussed in the depression section. [29]

#### Supportive and Palliative Care of Pancreatic Cancer

- Pain Management
- Intestinal Obstruction
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#### Pancreatic Insufficiency

##### ➤ Incidence

- Pancreatic insufficiency is common but moderate in patients with pancreatic cancer
  - ✓ 65% will have some degree of fat malabsorption
  - ✓ 50% will have some degree of protein malabsorption

##### ➤ Presentation

- Patients usually have weight loss, epigastric discomfort, flatulence, diarrhea, steatorrhea, and weight loss

##### ➤ Treatment

- A placebo-controlled trial randomized in patients with unresectable pancreatic cancer (8 weeks of oral high-dose enteric-coated pancreatic enzyme vs. placebo) prior to stenting [30]
- 1.2% ↑ in body weight in patients on enzymes vs. 3.7% ↓ in body weight in those on placebo
- Pancreatic duct stenting can be a useful in palliating obstructive symptoms and improve nutritional status

[30] Bruno MJ, et al. Gut 1998; 42:92-6.

Pancreatic exocrine insufficiency is common in patients with pancreatic cancer, usually after surgery. Pancreatic insufficiency may cause vague abdominal discomfort, pain, abdominal distention, excessive flatus (gas), belching, diarrhea, steatorrhea (fat indigestion) and weight loss. Pancreatic enzyme replacement has a unique role in management. It is obvious that pancreatic insufficiency is likely to be a problem with patients who have undergone surgery to have part of the pancreas removed. However, most non-surgical cancer patients will have a blocked or partially blocked pancreatic duct and so are also likely to have some need of enzyme replacement therapy. The benefit to non-surgical patients has been shown in a trial reported by Bruno *et al.* in 1998 [30]. It should be considered for most of the patients.

#### Challenges with Pancreatic Enzymes Replacement

- Activities of pancreatic enzymes decrease during their passage from the duodenum to the terminal ileum, but degradation rates of individual enzymes are different:
  - Lipase activity is lost most rapidly
  - Proteases and amylase are more stable
- Mechanism by which lipase activity is destroyed: **proteolysis** by the action of chymotrypsin. This mechanism is also operative in patients with chronic exocrine pancreatic insufficiency. It explains why fat malabsorption develops earlier compared with protein or starch malabsorption
- The substitution of lipase is also more difficult than that of other enzymes, because it is more rapidly destroyed by proteases
- Other factors that contribute to problems in lipase substitution therapy include:
  - acid-peptic destruction of unprotected enzyme preparations
  - unphysiological particle sizes of enteric-coated capsules or pellets

#### Pancreatic Insufficiency

- The development of microencapsulated enteric-coated spheres provided a major therapeutic advance in controlling absorption in cystic fibrosis patients. These newer formulations release enzymes at a pH of about 5.6, preventing their destruction in the stomach and delivering more bioactive enzymes to the duodenum
- Substitution of lipase to eliminate steatorrhea is the most important aim
- Empiric pancreolipase replacement should be considered for most patients
- **Dose.** In general, on the basis of the average reduction in total faecal fat excretion, the following doses have been suggested:
  - patients with chronic pancreatitis and prior Whipple's procedure (360,000 u lipase/day) may require higher doses than in patients with an intact upper gastrointestinal tract (100,000 u lipase/day)

Pancreatic enzyme replacement therapy should be considered if the patient develops any of the symptoms described earlier. Newer enteric-coated have better tolerability and efficacy. Anti-acid medications should make the enzymes more effective.



Various Pancreatic Enzymes Replacement		
Medication	Dose	Cost
Pancrelipase (acid resistant micro pellet): Creon® 5, Creon® 10, Creon® 20, Ku-zyme HP®	<ul style="list-style-type: none"> <li>Dosage varies according to the condition treated and diet of the patient.</li> <li>Approx 8,000 USP<sup>a</sup> units of lipase activity for each 17 gram of fat</li> <li>Usual initial dose is 4,000-33,000 USP<sup>a</sup> units of lipase activity (1-3 capsules or tablets)</li> </ul>	Creon® 10: 33.2-10-37.5 <i>ku</i> ® enteric coated capsules 100 capsules \$94.43, or 300 capsules \$271.62 Ku-zyme HP 30-8-30 <i>ku</i> ®: 100 capsules \$70.15 or 300 capsules \$200.25
Pancreatin Kustrase®	<ul style="list-style-type: none"> <li>Usual initial dose is approximately 8,000-24,000 USP<sup>a</sup> units of lipase activity before or with meals</li> </ul>	Kustrase 30-24-30 <i>ku</i> ®: 100 capsules \$ 88.80, or 300 capsules \$249.75

<sup>a</sup> USP : United States Pharmacopeia  
<sup>b</sup> *ku*: amylase-lipase-protease enzyme activity units  $\approx$  1,000

Replacement pancreatic enzymes are available in different formulations and dosages. For instance Creon® is available in dosages of 10,000, 25,000 and 40,000 units of lipase per capsule. So a patient needing a large quantity of enzymes per meal can take a smaller number of high dosage capsules (up to five or six capsules, around 240,000 units of lipase, with meals if necessary). Some patients, e.g. those who have had surgery to remove part or all of the pancreas, may need to take up to 20-30 of the high dosage capsules a day (i.e. 1,000,000 units of lipase). Price of the supplement can be another reason affecting the selection. In addition, if a patient is having problems with bloating despite taking the enzymes, changing to a different formulation may help few patients.

Pancreatic Enzymes Replacement
<p>➤ <b>How much dose to start?</b></p> <ul style="list-style-type: none"> <li>Initially prescribe one or two capsules of low dosage enzymes with meals Adjust the amount until there is some control of the symptoms such as diarrhea and steatorrhea</li> <li>The amount of pancreatic enzymes required will vary with amount of food eaten and may need to be increased with larger meals (e.g., 2 with meal and 1 with snack)</li> <li>It may take several adjustments before the most appropriate dosage is determined</li> </ul> <p>➤ <b>When to take?</b></p> <ul style="list-style-type: none"> <li>Best way is to take the enzymes throughout the meal or at the beginning, during and at the end of the meal so that they mix as much as they can with the food and travel along the digestive system with the food</li> </ul> <p>➤ <b>What if symptoms do not improve?</b></p> <ul style="list-style-type: none"> <li>Some patients can benefit by changing to a different formulation</li> <li>Change time of dose relative to food: taking them with meals or just after meals may help</li> </ul>

Replacement pancreatic enzymes are available in different formulations and dosages. If a patient needs a large quantity of enzymes per meal, he/she can take a smaller number of high dosage capsules or tablets.

Supportive and Palliative Care of Pancreatic Cancer
<ul style="list-style-type: none"> <li>➤ Pain Management</li> <li>➤ Intestinal Obstruction</li> <li>➤ Biliary Obstruction</li> <li>➤ Depression</li> <li>➤ Fatigue</li> <li>➤ Pancreatic Insufficiency</li> <li>➤ Cachexia</li> </ul>

Cachexia
<ul style="list-style-type: none"> <li>➤ Cancer-anorexia-cachexia is one of the most common causes of death in patients with cancer [31]</li> <li>➤ <b>Etiology:</b> it is related to direct and indirect metabolic abnormalities produced by the tumor that leads to anorexia. These abnormalities also results in lipolysis, protein loss and anorexia leading to cachexia</li> <li>➤ Cachexia often contributes to depression and is a predictive of poor outcome and poor quality of life [32]</li> <li>➤ <b>Pathogenesis:</b> cachexia is a result of cytokines released by the tumor</li> <li>➤ TNF alpha, interleukin 1B, interleukin 6, ciliary neurotropic factor and proteolysis inducing factor are incriminated in pathogenesis [33]</li> </ul> <p>[31] Nelson KA. Curr Oncol Rep 2000; 2:362-8.            [32] Jatoti A Jr, Loprinzi CL. Oncology (Williston Park) 2001; 15:497-502.            [33] Uomo G, et al. JOP. J Pancreas (Online) 2006; 7:157-62.</p>

The cancer-anorexia-cachexia syndrome is complex and incompletely understood. Supplemental feeding by parenteral and oral routes does not result in reversal of the cancer-anorexia-cachexia. It is difficult to separate the symptom (anorexia) from the sign (cachexia) in the dynamic process leading to cancer-anorexia-cachexia syndrome. The disease burden does not correlate with cachexia. [31, 32, 33]

Management of Cachexia
<ul style="list-style-type: none"> <li>➤ <b>Supportive nutrition, caloric supplementation and hydration, preferably orally</b> <ul style="list-style-type: none"> <li>• Parenteral nutrition, when appropriate</li> </ul> </li> <li>➤ Management of pancreatic insufficiency is important</li> <li>➤ Assessment of anorexia to identify any correctable cause such as gastrointestinal dysmotility, nausea, vomiting, constipation, taste change, dry mouth, depression or food aversion</li> </ul>

Supportive nutrition with caloric supplementation using oral route is important. This method is associated with lesser side effects as compared to parenteral route. Parenteral route is associated with infection, thrombosis and metabolic abnormalities. It is important to manage the patient for the exocrine pancreatic insufficiency. It is unusual for a patient with anorexia to have single specific contributing factor, when controlled alleviates the anorexia.

### Management of Cachexia

- **Pharmacological intervention** with appetite stimulant can be helpful
  - *Dexamethasone*, side effects can be troublesome especially when duration of treatment is longer than 3 weeks. Short lived duration of action (4 weeks)
  - *Megestrol* well studied and used agent. It causes weight gain in approximately 15% of patient
  - *Dronabinol* has been shown to improve chemotherapy induced nausea and vomiting in 65% of cancer patients
  - *Metoclopramide* is used as a prokinetic agent
- *Thalidomide* provide some weight stabilization but no weight gain
- *Ibuprofen* may lead to modest increase in weight

Pharmacological interventions using appetite stimulants, prokinetic agents and newer agents can be helpful. The appetite stimulants such as megesterol, dexamethasone have been shown to act rapidly and increase non fluid body weight in patients with advanced cancer. Dronabinol has been shown to be effective in HIV associated cachexia as well.

### Management of Cachexia

Medications	Dose
<i>Dronabinol</i>	Start at 2.5 mg every 8 hours daily with meals; increase the dose up to 5 mg every 8 hours daily (as tolerated)
<i>Metoclopramide</i>	Start at every 6 hours; administer 30 minutes before meals and at bed time
<i>Dexamethasone</i>	Start at 4 mg po daily and increase to 8 mg twice daily
<i>Megestrol acetate</i>	Start at 80 mg every 12 hours after meals; escalate to 200 mg every 6 hours daily (as tolerated)
<i>Thalidomide</i>	Start at 50 mg at bed time. Maintenance dose is 100-200 mg/day
<i>Eicosapentaenoic acid</i>	Usual dose is 1-6 g/day
<i>Oxandrolone</i>	2.5-20 mg/day in divided doses two-four times/day

Various drugs, such as dronabinol, metoclopramide, dexamethasone, and others

can be used to manage cachexia. Patient's other co-morbid conditions as well as other medications (drug-drug interaction) should be assessed before prescribing a medication to manage cachexia.

### Omega-3 Fatty Acids for Cancer Cachexia [34]

- **Common names:** fish oil, fish oil supplements, marine oil, cod liver oil
- **Scientific name:** alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. This group is also called n-3 fatty acids, or n-3 polyunsaturated fatty acids
- **Source:** the body cannot make these fatty acids and must obtain them from food sources or from supplements. Three fatty acids compose the omega-3 family *Alpha-linolenic acid (ALA)* is found in English walnuts and in canola, soybean, flaxseed/linseed, and olive oil
  - *Eicosapentaenoic acid (EPA)* and *docosahexaenoic acid (DHA)*, are found in fish, including fish oil and supplements
- **Role:** omega-3 polyunsaturated fatty acid have been shown to modulate proinflammatory cytokines, hepatic acute phase proteins, eicosanoids and tumor derived factors in animal models

[34] Harle L, et al. J Altern Complement Med 2005; 11:1039-46.

Omega-3 fatty acids are important nutrients that are involved in many bodily processes. Our bodies cannot manufacture these fatty acids and therefore, must obtain them from food sources (or from supplements). There are three fatty acids that compose the omega-3 family: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It is important to note that omega-3 fatty acids are different from the omega-6 fatty acids, which are also essential. Unlike omega-3s, omega-6s are quite plentiful in the typical US diet. [34]

### Omega-3 Fatty Acids for Cancer Cachexia

- **Clinical data**
  - *Omega 3 acid ethyl esters* is the only FDA approved prescription omega-3 fatty acid product
  - Three phase 3 trials did not show any benefit of omega 3 fatty acids [35]
  - Recent double blind, placebo controlled study by Fearon et al. [36] showed no statistically significant benefit from single agent eicosapentaenoic acid
- **Possible toxicity**
  - Not enough is known about omega-3 fatty acids to determine if they are safe in large quantities or in the presence of other drugs
    - ✓ *Omega-3s* may increase total blood cholesterol and inhibit blood clotting
    - ✓ People who take anticoagulant drugs or aspirin should not consume additional amounts of omega-3 because of the risk of excessive bleeding
  - Source of some omega-3 fatty acids may be a health concern
    - ✓ Many larger predatory fish contain toxins absorbed from pollution

[35] Jatoi A. Nutr Clin Pract 2005; 20:394-9.

[36] Fearon KC, et al. J Clin Oncol 2006; 24:3401-7.

Omega-3 acid ethyl esters is the only FDA approved prescription omega-3 fatty acid product. [35, 36]



### Conclusions

- Pancreatic cancer is a model illness that mandates the need for good supportive and palliative treatment
- Pain may be linked with depression and anxiety. The mainstay of pain therapy are analgesic drug therapy and interventional anesthetic blocks
- Interventional pain management techniques should not be considered as last resort in pain management
- Biliary obstruction can be successfully palliated with endoscopic stent placement in selected patients
- Surgical interventions are usually considered futile in patients with intestinal obstruction
- It is important to recognize the contributing factors of fatigue in patient with cancer
- Empiric pancreolipase supplementation should be considered for most of the patients
- There was significant correlation between increasing pain and depression and between pain and depressive symptoms and impaired quality of life
- Although there is no treatment for cancer anorexia cachexia pharmacological and non pharmacological treatment can enhance food intake and improve quality of life
- Palliative and supportive care of cancer patient is at the very heart of oncology

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**Keywords** Cachexia; capecitabine; Cholestasis; Depression; Exocrine Pancreatic Insufficiency; gemcitabine; Intestinal Obstruction; Jaundice; Nerve Block; Pain; Pancreas; Pancreatic Neoplasms; Stents

**Abbreviations** SES: self expandable stents; SSRI: selective serotonin reuptake inhibitor

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