JOP. J Pancreas (Online) 2007; 8(2):240-253.

HIGHLIGHT ARTICLE - Slide Show

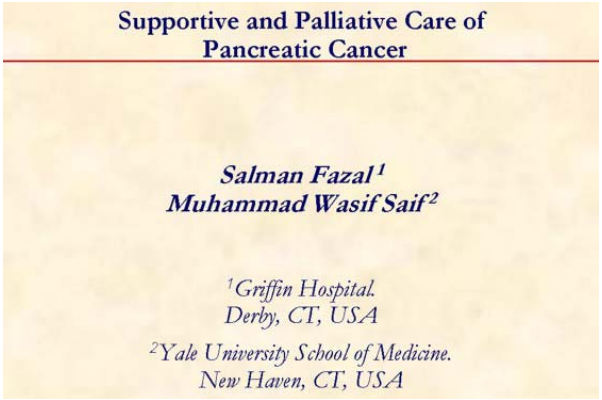
Supportive and Palliative Care of Pancreatic Cancer

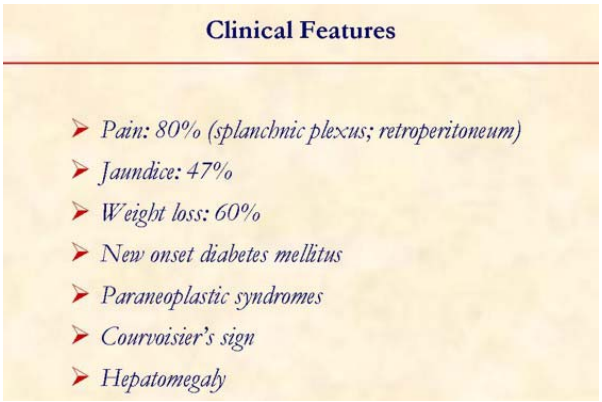
Salman Fazal[1], Muhammad Wasif Saif[2]

[1]Griffin Hospital. Derby, CT, USA. [2]Yale University School of Medicine. New Haven, CT, USA

Summary

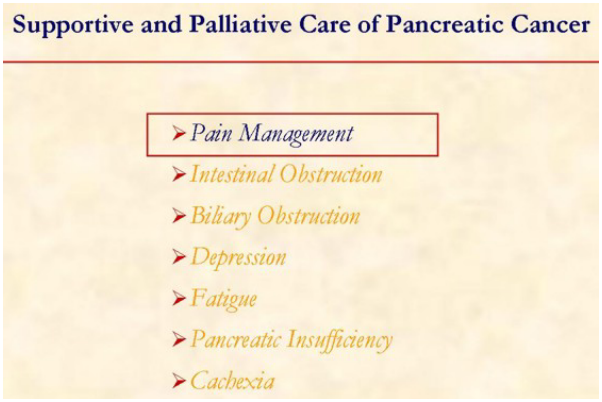
Pancreatic cancer is one of the most lethal malignancies. An estimated 32,300 patients will die of pancreatic cancer in year 2006. It is the tenth most common malignancy in the United State. Despite recent advances in pathology, molecular basis and treatment, the overall survival rate remains 4% for 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.



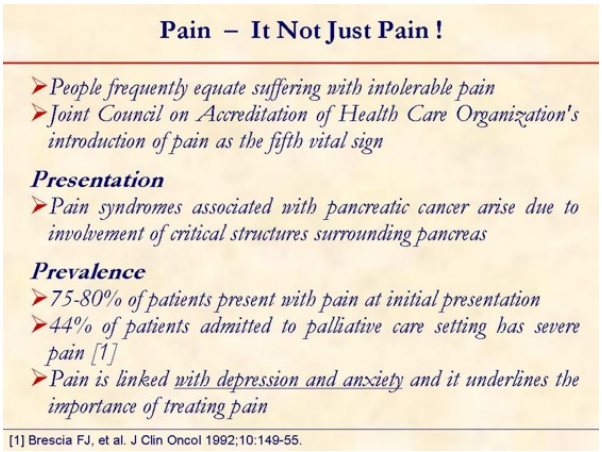


The presenting symptoms of pancreatic cancer can include pain, unexplained weight loss, nausea, vomiting, steatorrhea, dyspepsia, depression and jaundice. There are no well known warning signs of pancreatic cancer. However, new onset diabetes in an old patient has been associated with pancreatic cancer.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

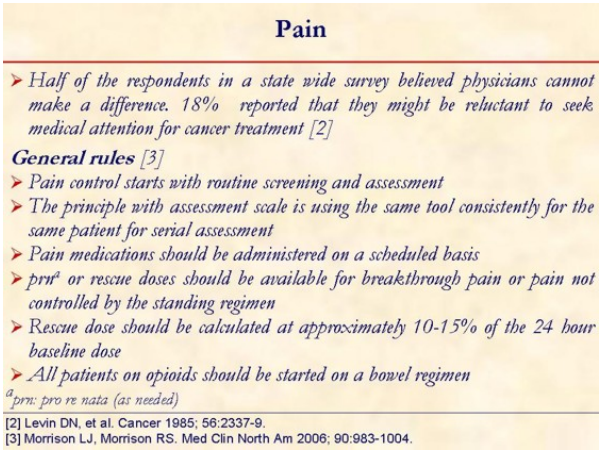
the typical presentation of pancreatic cancer, most of the patient have mild to moderate abdominal pain. Back pain usually suggests involvement of retroperitoneal nerves. Jaundice usually develops in patient with tumor in the head of pancreas, on the other hand , tumor in the tail of pancreas do not 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.



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



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]



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]

In addition to above medications steroids, anticonvulsants, antidepressants and biphosphonates 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*

Stool softeners	*Docusate sodium, calcium docusate*
Stimulant laxatives	*Prune juice, senna, bisacodyl*
Osmotic laxatives	*Lactulose, propylene glycol, milk of magnesia, magnesium citrate*
Miscellaneous	*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
Docusate	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
Senna	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.
Bisacodyl	Oral: 5-15 mg/day. Rectal: suppository 10 mg as single dose	Effect occur in 6-10 h.
Lactulose	Oral: 10-20 g/day, may increase to 40 g/day in divided doses	
Milk of magnesia	Liquid: 30-60 mL/day in divided doses Tablets: 6-8 tablets/day	Use with caution in patients with impaired renal function
Magnesium citrate	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

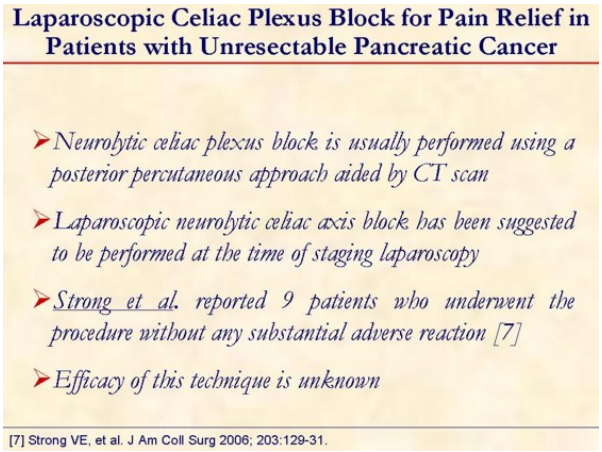
Common reasons for failure

- *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*

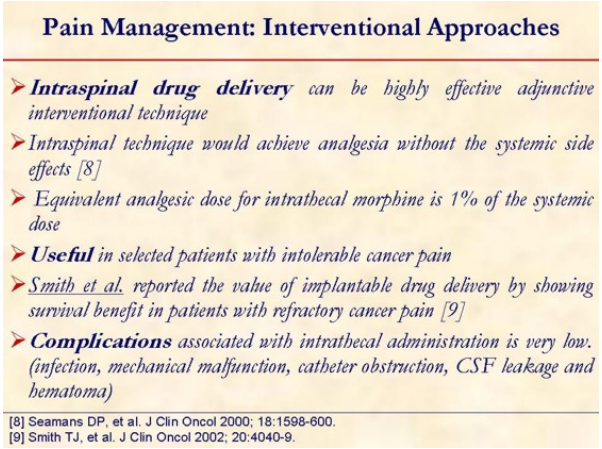
It is important to know the common reasons for inadequate pain control. Pain control is better with scheduled or around the clock dosing. Tolerance and dependence are pharmacological properties of pain

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.

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]

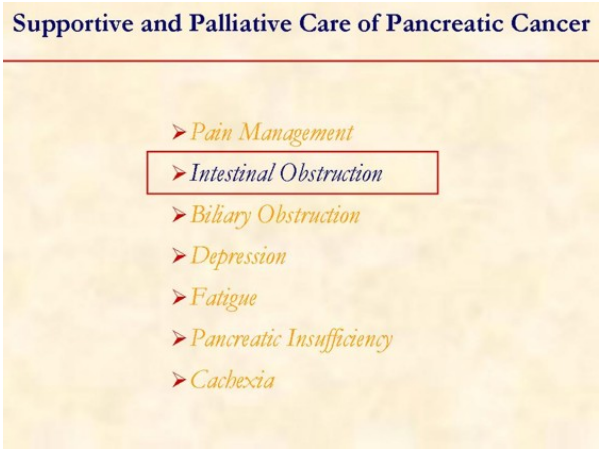


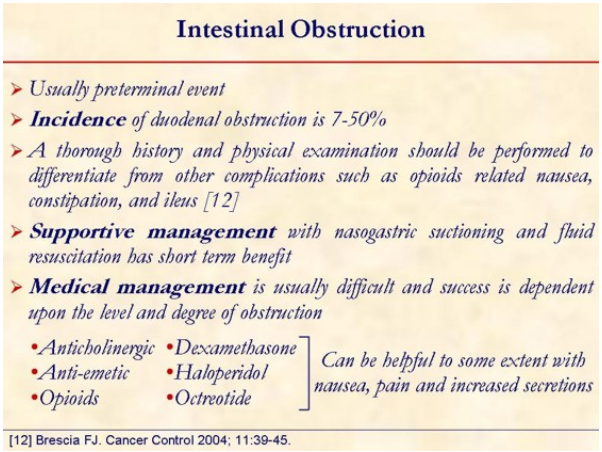
Neurolytic celiac plexus block is usually performed using a posterior percutaneous approach aided by CT scan. On the other hand, laparoscopic neurolytic celiac axis block can be performed at the time of staging laparoscopy. [7]



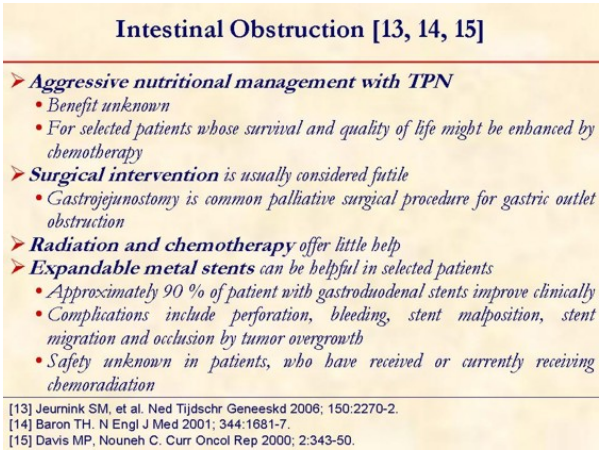
Intraspinal drug delivery via intrathecal or epidural route can be useful interventional technique. It allows to decrease the systemic side effects of oral opioids therapy. The economic issue can be an additional consideration favoring its use over the systemic analgesic therapy. However, intraspinal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

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]

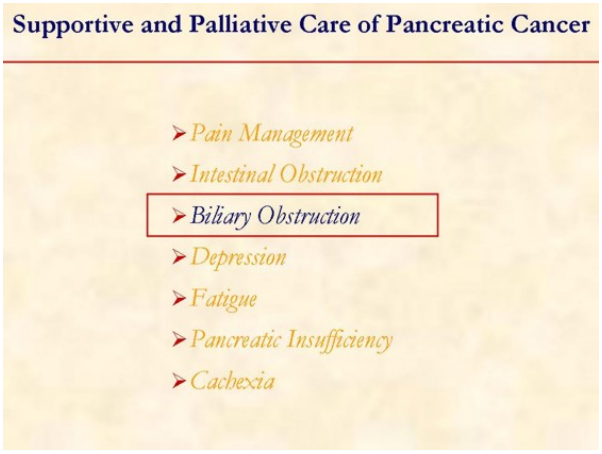


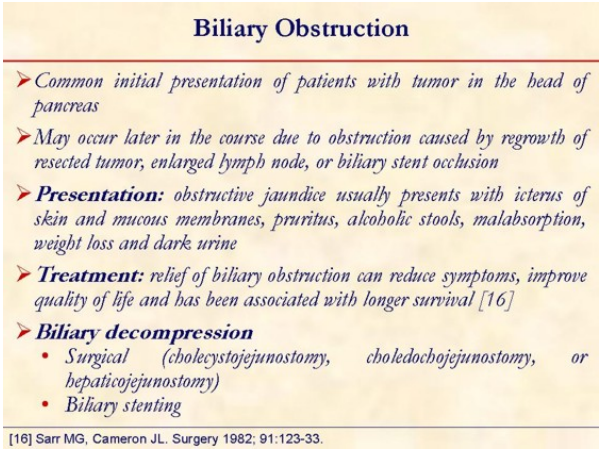


Intestinal obstruction is a late complication of advanced pancreatic cancer. It is important to evaluate for other causes which can present in similar way. Nasogastric suctioning can decompress the bowel and relieve some of the abdominal distention and pain. Pharmacological interventions can be helpful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



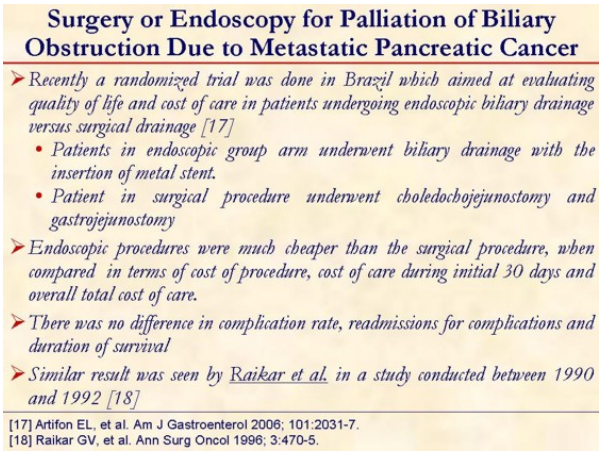
No data are available to support the use of aggressive parenteral nutrition in patient with advanced terminal disease. The advantage of surgical intervention such as gastro-jejunostomy is long term efficacy. A disadvantage is prolonged postoperative course. Endoscopic stent placement can be helpful in 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]



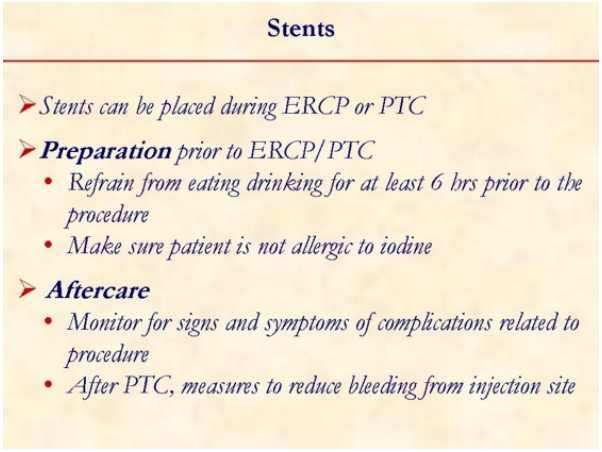


Around 90% of patients will have jaundice during some stage of their illness. The optimal management of these patients will vary depending upon their age, life expectancy, performance status, potential resectability of the tumor and physician's expertise. Surgical decompression may be the best option 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]



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].



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 note mentioned over here.

Biliary Obstruction

- Most patients are best palliated with stent placement
- **Endoscopic stent placement** is preferred over percutaneous approach [19]
- **Expandable or Teflon® stent versus a plastic stent** - practical decision [20]
- **Prophylactic bypass procedures** are not useful
- Recent data shows that newly designed plastic stents (Tannenbaum) has better duration of patency than the polyethylene stent

[19] Speer AG, et al. Lancet 1987; 2:57-62.
[20] Haringsma J, Huibregtse 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

- 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
- 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)
- Tannenbaum stents can be a reasonable option for patients with liver metastasis and expected short survival time

[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 Polyethylene[a] Polyurethane Teflon Double layer Tannenbaum	• Less expensive as compared to metal stents. Reasonable choice in patient with advanced disease and reduced survival (3-6 months) • Tannenbaum stents has better patency rate as compared to polyethylene stents • May be used to assess the patency of occluded metallic stent
Metal	Nitinol Elgiloy (Membrane-coated metal stents are also used)	• Patients with longer expected survival >6 months should have SES[b] • 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 • Removal of metallic stent is virtually impossible • Usually the stent of choice to open occluded plastic stents • In patients with several comorbidities where it is not feasible to have second ERCP • Open mesh design of metallic stent in patients with biliary obstruction allows continued patency of contralateral ducts

[a] Polyethylene stents are the most common type of plastic stents
[b] SES: self expandable stents

Characteristics of Stents (II)

Type	Make up	Life time [22]	Complications [b]
Plastic	Nylon	-	• Stent occlusion (increased as compared to metal stents)
	Polyethylene [a]	75.5 -142 days	• Stent migration
	Polyurethane	-	• Stent fracture (rare)
	Teflon	83-181 days	
	Double layer	-	
	Tannenbaum	123.5 days Risk of occlusion increases progressively after 3 months	
Metal	Nitinol Elgiloy (Membrane-coated metal stents are also used)	111-273 days	• Stent occlusion • Stent migration • Stent fracture

[a] Polyethylene stents are the most common type of plastic stents
[b] 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]

Supportive and Palliative Care of Pancreatic Cancer

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

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

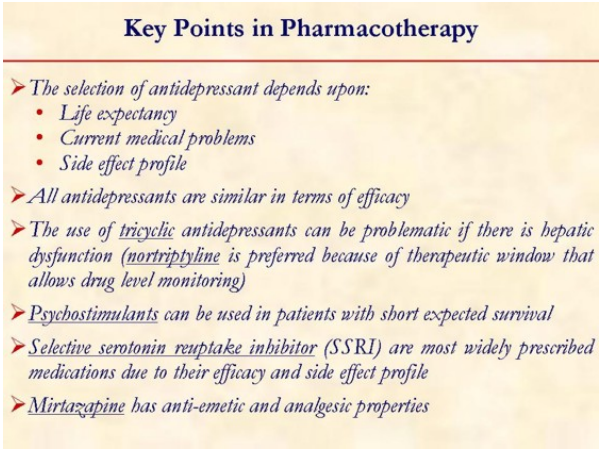
Antidepressants	Dose (mg; starting and usual dose)	Adverse reactions
Amitriptyline	25-50 , 100-300	Drowsiness, drymouth, constipation, confusion, sexual dysfunction, urinary retention, seizure
Nortriptyline	25 , 50-200	Same as above
Citalopram	20 , 20-60	Drowsiness, insomnia, headache, nausea, vomiting, 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 .....

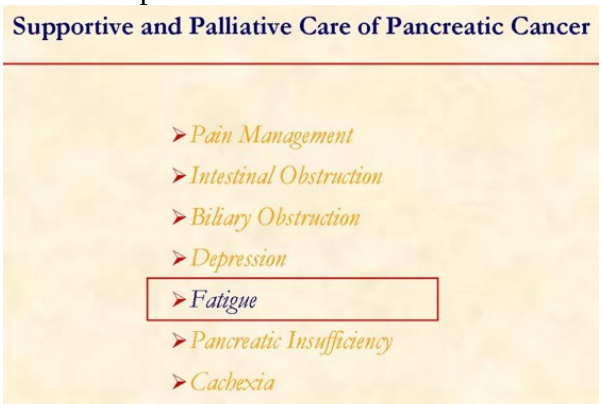
..... continued.

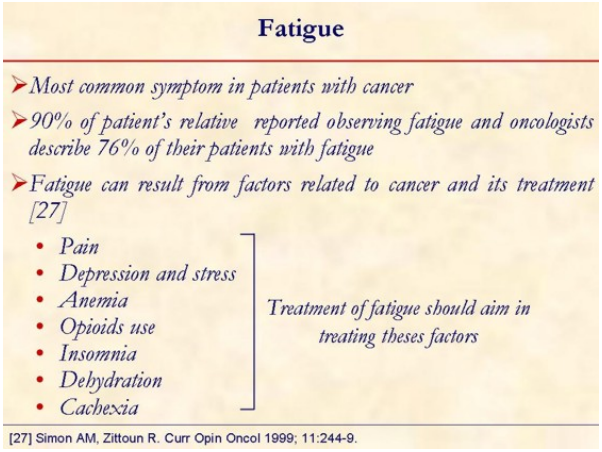
Antidepressants	Dose (mg; starting and usual dose)	Adverse reactions
Sertraline	50 , 50-100	Nausea, vomiting, diarrhea, insomnia, sexual dysfunction, nervousness
Bupropion	150 , 300-450	Tachycardia, headaches. insomnia, weight loss, seizures, dizziness
Venlafaxine	37.5 , 75-300	Weakness, diaphoresis, 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.

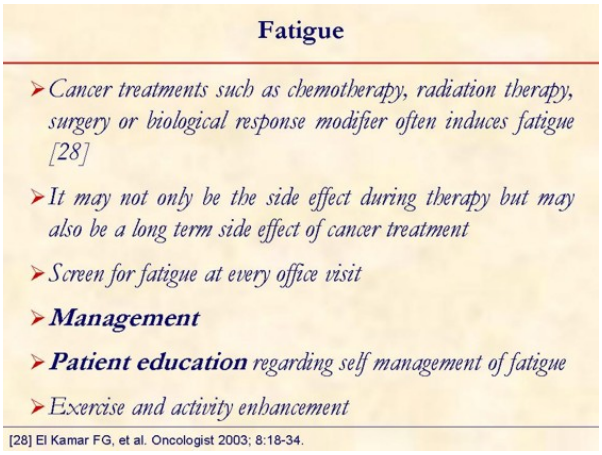


The clinical trials have shown that all the antidepressants are approximately equal in terms of the efficacy. The choice of the antidepressants is dependent on the current medical problems, their side effect profile and life expectancy of the patient. It is important to identify the side effect profile 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.





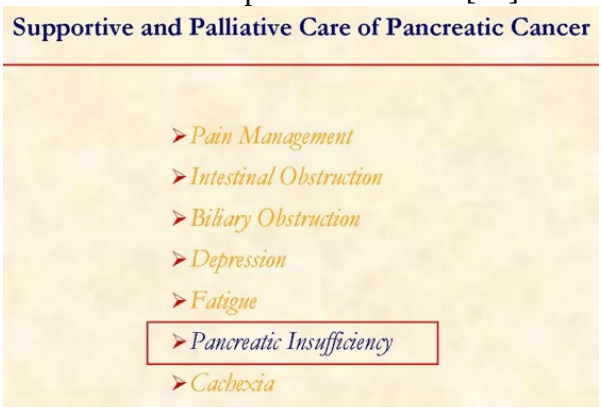
Cancer related fatigue is a subjective experience of tiredness that can influence the patient's ability to continue with the treatment and eventually can decrease the chance of antitumor effect of chemotherapy. It is important to recognize the several contributing factors outline above in each patient.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

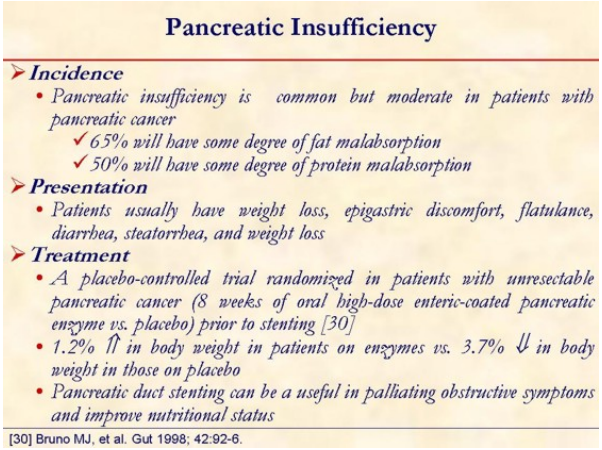


Causes of cancer related fatigue are diverse and are partially explained. Fatigue has been associated with chemotherapy. It has been found that fatigue is usually intense in first few days after chemotherapy. It usually abates over the next few days. Sometimes it can last for prolonged period after the 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

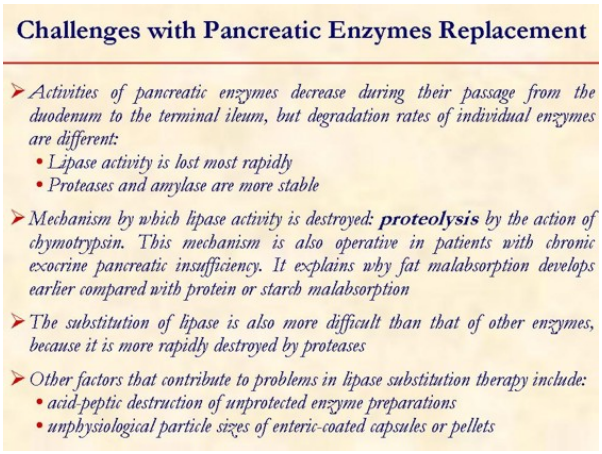
that patient can prioritize their activities, so that fatigue does not prevent them from performing essential activities. Exercise and activity enhancement has been shown consistently to help in fatigue. It increases the functional capacity so that they can perform their activities with reduced effort.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

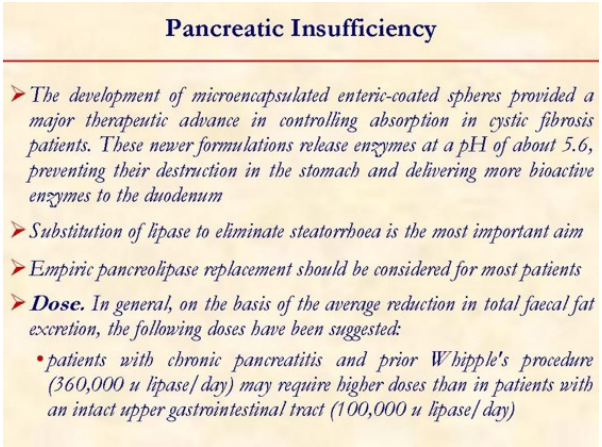
Pharmacological therapy can be helpful in certain subsets of patients. Erythropoietin can improve hematocrit and increase the energy level in patients with anemia. Psycho-stimulants can reduce fatigue and depression in patients with malignancy. The side effects of methylphenidate and pemoline have been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





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.





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 ®	• Dosage varies according to the condition treated and diet of the patient. • Approx 8,000 USP[a] units of lipase activity for each 17 gram of fat • Usual initial dose is 4,000-33,000 USP[a] units of lipase activity (1-3 capsules or tablets)	Creon® 10: 33.2-10-37.5 kuˈ enteric coated capsules: 100 capsules $94.43, or 300 capsules $271.62 Ku-zyme HP 30-8-30 kuˈ: 100 capsules $70.15 or 300 capsules $200.25
Pancreatin Kutrase®	• Usual initial dose is approximately 8,000-24,000 USP[a] units of lipase activity before or with meals	Kutrase 30-2.4-30 kuˈ: 100 capsules $ 88.80, or 300 capsules $249.75

[a] USP : United States Pharmacopeia
[b] ku: amylase-lipase-protease enzyme activity units x 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

- **How much dose to start?**
  - 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
  - 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)
  - It may take several adjustments before the most appropriate dosage is determined
- **When to take?**
  - 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
- **What if symptoms do not improve?**
  - Some patients can benefit by changing to a different formulation
  - Change time of dose relative to food: taking them with meals or just after meals may help

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

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

Cachexia

- Cancer-anorexia-cachexia is one of the most common causes of death in patients with cancer [31]
- **Etiology:** 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
- Cachexia often contributes to depression and is a predictive of poor outcome and poor quality of life [32]
- **Pathogenesis:** cachexia is a result of cytokines released by the tumor
- TNF alpha, interleukin 1B, interleukin 6, ciliary neurotropic factor and proteolysis inducing factor are incriminated in pathogenesis [33]

[31] Nelson KA. Curr Oncol Rep 2000; 2:362-8.
[32] Jatoi A Jr, Loprinzi CL. Oncology (Williston Park) 2001; 15:497-502.
[33] Uomo G, et al. JOP. J Pancreas (Online) 2006; 7:157-62.

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

- **Supportive nutrition**, caloric supplementation and hydration, preferably orally
  - Parenteral nutrition, when appropriate
- Management of pancreatic insufficiency is important
- Assessment of anorexia to identify any correctable cause such as gastrointestinal dysmotility, nausea, vomiting, constipation, taste change, dry mouth, depression or food aversion

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*
  - *Metoclopromide 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
Dronabinol	Start at 2.5 mg every 8 hours daily with meals; increase the dose up to 5 mg every 8 hours daily (as tolerated)
Metoclopramide	Start at every 6 hours; administer 30 minutes before meals and at bed time
Dexamethasone	Start at 4 mg po daily and increase to 8 mg twice daily
Megestrol acetate	Start at 80 mg every 12 hours after meals; escalate to 200 mg every 6 hours daily (as tolerated)
Thalidomide	Start at 50 mg at bed time. Maintenance dose is 100-200 mg/day
Eicosapentaenoic acid	Usual dose is 1-6 g/day
Oxandrolone	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 assesses 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.

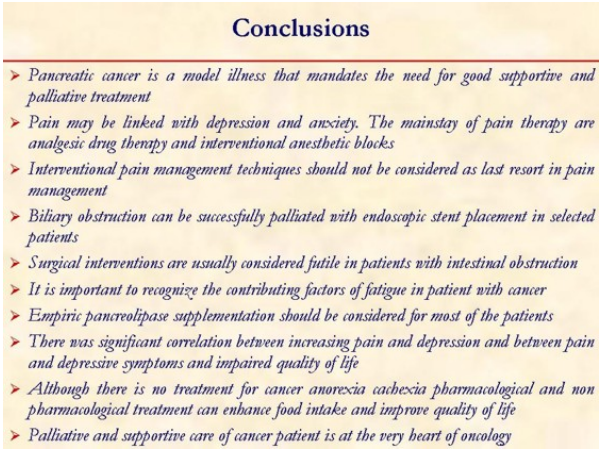
Omega-3 fatty acids are important nutrients that are involved in many bodily processes. Our bodies cannot manufacture these fatty acids and therefore, must obtain them from food sources (or from supplements). There are three fatty acids that compose the omega-3 family: alpha-linolenic acid (ALA), eicosapentaenoic 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]



Received December 15th, 2006 - Accepted January, 16th

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

Correspondence
Muhammad Wasif Saif
Yale University School of Medicine
Section of Medical Oncology
333 Cedar Street, FMP 116
New Haven, CT 06520
USA
Phone: +1-203.737.1875
Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

Document URL: http://www.joplink.net/prev/200703/07.html

References

1. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 1992; 10:149-55. [PMID 1345797]

2. Levin DN, Cleeland CS, Dar R. Public attitudes toward cancer pain. Cancer 1985; 56:2337-9. [PMID 2865000]

3. Morrison LJ, Morrison RS. Palliative Care and Pain Management. Med Clin North Am 2006; 90:983-1004. [PMID 16962853]

4. McDonnell FJ, Sloan JW, Hamann SR. Advances in Cancer Pain Management. Curr Oncol Rep 2000; 2:351-7. [PMID 11122864]

5. Staats PS, Hekmat H, Sauter P, Lillemoe K. The effects of alcohol, celiac plexus block, pain, and mood on longevity in patients with unresectable pancreatic cancer: a double-blind, randomized, placebo-controlled study. Pain Med 2001; 2:28-34. [PMID 15102315]

6. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993; 217:447-55. [PMID 7683868]

7. Strong VE, Dalal KM, Malhotra VT, Cubert KH, Coit D, Fong Y, Allen PJ. Initial report of laparoscopic celiac plexus block for pain relief in patients with unresectable pancreatic cancer. J Am Coll Surg 2006; 203:129-31. [PMID 16798497]

8. Seamans DP, Wong GY, Wilson JL. Interventional Pain therapy for intractable abdominal cancer pain. J Clin Oncol 2000; 18:1598-600. [PMID 10735909]

9. Smith TJ, Staats PS, Deer T. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002; 20:4040-9. [PMID 12351602]

10. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15:2403-13. [PMID 9196156]

11. Saif MW, Eloubeidi MA, Russo S, Steg A, Thornton J, Fiveash J, et al. Phase I study of capecitabine with concomitant radiotherapy for patients with locally advanced pancreatic cancer: expression analysis of genes related to outcome. J Clin Oncol 2005; 23:8679-87. [PMID 16314628]

12. Brescia FJ. Palliative care in pancreatic cancer. Cancer Control 2004; 11:39-45. [PMID 14749622]

13. Jeurnink SM, Steyerberg EW, van Eijck CH, Kuipers EJ, Siersema PD. Gastrojejunostomy versus endoscopic stent placement as palliative treatment for malignant constriction of the duodenum: the SUSTENT study. Ned Tijdschr Geneeskd 2006; 150:2270-2. [PMID 17076365]

14. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the

gastrointestinal tract. N Engl J Med 2001; 344:1681-7. [PMID 11386268]

15. Davis MP, Nouneh C. Modern management of cancer related intestinal obstruction. Curr Oncol Rep 2000; 2:343-50. [PMID 11122863]

16. Sarr MG, Cameron JL. Surgical management of unresectable carcinoma of the pancreas. Surgery 1982; 91:123-33. [PMID 6173929]

17. Artifon EL, Sakai P, Cunha JE, Dupont A, Filho FM, Hondo FY, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. Am J Gastroenterol 2006; 101:2031-7. [PMID 16968509]

18. Raikar GV, Melin MM, Ress A, Lettieri SZ, Poterucha JJ, Nagorney DM, Donohue JH. Cost effective analysis of surgical palliation versus endoscopic stenting in the management of unresectable pancreatic cancer. Ann Surg Oncol 1996; 3:470-5. [PMID 8876889]

19. Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, et al. Randomized trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987; 2:57-62. [PMID 2439854]

20. Haringsma J, Huibregtse K. Biliary stenting with a prototype expandable Teflon endoprosthesis. Endoscopy 1998; 30:718-20. [PMID 9865563]

21. Katsinelos P, Paikos D, Kountouras J, Chatzimavroudis G, Paroutoglou G, Moschos I, et al. Tannenbaum and metal stents in the palliative treatment of malignant distal bile duct obstruction: a comparative study of patency and cost effectiveness. Surg Endosc 2006; 20:1587-93. [PMID 16897286]

22. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006; 2:CD004200. [PMID 16625598]

23. Fras I, Litin EM, Pearson JS. Comparison of psychiatric symptoms in carcinoma of the pancreas with those in some other intra-abdominal neoplasms. Am J Psychiatry 1967; 123:1553-62. [PMID 4381627]

24. Joffe RT, Rubinow DR, Denicoff KD, Maher M, Sindelar WF. Depression and carcinoma of the pancreas. Gen Hosp Psychiatry 1986; 8:241-5. [PMID 3744031]

25. Kelsen DP, Portenoy RK, Thaler HT, Niedzwiecki D, Passik SD, Tao Y, et al. Pain and depression in patients with newly diagnosed pancreativc cancer. J Clin Oncol 1995; 13:748-55. [PMID 7884435]

26. Angelino AF, Treisman GJ. Major depression and demoralization in cancer patients; diagnosis and treatment considerations. Support Care Cancer 2001; 9:344-9. [PMID 11497387]

27. Simon AM, Zittoun R. Fatigue in cancer patients. Curr Opin Oncol 1999; 11:244-9. [PMID 10416875]

28. El Kamar FG, Grossbard ML, Kozuch PS. Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. Oncologist 2003; 8:18-34. [PMID 12604729]

29. Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue: evolving concepts in evaluation and treatment. Cancer 2003; 98:1786-801. [PMID 14584059]

30. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 1998; 42:92-6. [PMID 9505892]

31. Nelson KA. Modern management of the cancer anorexia-cachexia syndrome. Curr Oncol Rep 2000; 2:362-8. [PMID 11122866]

32. Jatoi A Jr, Loprinzi CL. Current management of cancer associated anorexia and weight loss. Oncology (Williston Park) 2001; 15:497-502. [PMID 11346935]

33. Uomo G, Gallucci F, Rabitti PG. Anorexia-cachexia syndrome in pancreatic cancer: recent development in research and management. JOP. J Pancreas (Online) 2006; 7:157-62. [PMID 16525199]

34. Harle L, Brown T, Laheru D, Dobs AS. Omega-3 fatty acids for the treatment of cancer cachexia: issues in designing clinical trials of dietary supplements. J Altern Complement Med 2005; 11:1039-46. [PMID 16398596]

35. Jatoi A. Omega 3 fatty acid supplements for cancer associated weight loss. Nutr Clin Pract 2005; 20:394-9. [PMID 16207679]

36. Fearon KC, Barber MD, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, Murray GD. Double blind, placebo-controlled, ranndomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol 2006; 24:3401-7. [PMID 16849754]