TREATMENT STRATEGIES FOR DIGESTIVE SYMPTOMS IN PANCREATIC CANCER

HEATHER WRIGHT ND FABNO
Most people with pancreatic cancer are diagnosed with advanced stage disease

- Fewer than 20% survive the 1st year, 3% survive 5 years, 10% resectable at diagnosis
  
  - **Resectable:** for tumors <2cm, 5 year survival after resection is 30%; for no residual tumor is 35%; no lymph node mets is 55%
  
  - **Non-resectable:** median survival 2-6 months, this is what most of our patients are told

Pancreatic cancer is projected to become the 2nd leading cause of cancer death by the year 2030 in the U.S.

Naturopathic medicine tools such as dietary education, behavioral counseling, and supplement interventions can support reduction in symptoms & impact quality of life (QoL)

**Improved QoL is correlated with survival benefit during standard treatment approach**

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WHAT CAN WE OFFER?

Start with education about digestive organs, physiology & diet. Diagram!

- Knowledge helps patients gain a sense of control = empowering
- Helps connect the rationale for daily interventions with benefit at the level of organ function

Prioritize tools that can help reduce pain/discomfort caused by symptoms

- Natural substances with vitro data against cancer cells? No!
- Bite for bite, pill for pill, prioritize supps & diet to support digestion/assimilation- YES!
- Compare benefit of pharma/phyto, use practical integrative interventions
- Screen for interactions among scripts and natural agents

Specific interventions that fit the precise symptom & disease picture can help make a difference in how the patient digests food, assimilates nutrients, impact energy levels, weight stability and help normalize bowels each day.

Frame each day. Feeling a little better each day is a great start.

Improving quality of life (as indicated by measures such as pain & fatigue) during treatment, is associated with improved survival.


Pancreatic ductal adenocarcinoma (75-90% of all dx)

- haphazard arrangement of neoplastic glands in desmoplastic stroma, ductal phenotype highly aggressive
- Up to 75% occur in the head
  - early biliary obstruction, jaundice, weight loss, diarrhea
- 9% in the body
- 8% in the tail
  - asymptomatic until late stage
- 6% in overlapping sites
- 20% extension to subsites

Other types of pancreatic cancer:
- Exocrine parenchymal = ductal
- Endocrine islet cell
- Non-epithelial (sarcomas and lymphomas – rare)
- Metastatic (from breast, lung, cutaneous melanoma, NHL)
- Becoming cancerous: >1 cm, high-grade dysplasia, predominately villous
Location of tumor often impedes function of ducts and pathways for blood flow, liver function, bile, enzymes, bicarbonate, and pancreatic juices that all lead to the duodenum.

Locations of tumor may correlate with symptoms.
PANCREATIC CANCER TAKES YEARS TO DEVELOP

• Begins with an initiating mutation in a normal cell followed by clonal expansion

• At least 10 years between the initiating mutation and the birth of the parental, non-metastatic founder tumor cell

• $\geq 5$ additional years required for metastatic ability

• Most patients are not diagnosed until metastatic sub-clones have already escaped the pancreas

THE HAND BASKET:
RISK FACTORS FOR PANCREATIC CANCER

Factors:

- Inherited Susceptibility
- Age - peak incidence in those > 60 years of age, median age of dx: 70
- BMI - > 25
- Lower socioeconomic status
- Smoking status - 2 x’s greater risk in heavy smokers
- Chronic pancreatitis - 3.6 x’s higher risk
- Type 2 diabetes - 51% higher risk
- Previous breast cancer - 38% higher risk
- Previous renal cancer - 97% higher risk

[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4368998/]
THE HAND BASKET CONT’D:

Other risk factors:

- **Red meat & processed meat**
  - An increase of 50g per day of processed meat consumption is associated with 19% increased risk
  - A statistically significant positive association between red meat consumption and risk (men only)

- **Partial-gastrectomy** (increased risk within 2 years of surgery, 2 x’s higher risk 15-20 years later)
  - Hypoacidity =proliferation of bacteria that produce nitrate reductase leading to increased formation of N-nitrose
  - In 2633 post gastrectomy patients an overall increased risk of 1.8 was observed. The risk gradually increases to 3.6 after a postoperative interval of 35 years or more.
  - Increased K-ras codon 12 mutations were found in postgastrectomy panc cancer cases

- **Excess cholecystokinin CCK** (increased in cholecystectomy and duodenogastric reflux)
  Clinical and Translational Gastroenterology (2016) 7, e134; doi:10.1038/ctg.2015.61; published online 7 January 2016

- **Exposures** –chemicals such as beta-naphthalene & benzidine. Pesticides: pendimethalin, trifluralin, EPTC, chlorimuron-ethyl, and heptachlor

- **Chronic alcohol consumption** associated with pancreatic cancer among men but not women, with increased risk ranging from 1.5- to 6-fold based on the dose, duration, and pattern

- **2 or more sodas per week**  Individuals consuming 2+ soft drinks/wk experienced a statistically significant increased risk
Some primary and secondary tx regimens for advanced pancreatic cancer &
their associated side effects:

• **Surgery** - considered the only potentially curative approach
  - pancreato duodenectomy, pyloris preserving whipple, extended whipple, distal/total
  pancreatectomy; if exploratory lap shows not resectable: palliative gastro-enterostomy en
  hepaticojejunostomy

• **Just Gem**: Gemcitabine, or combo prior to chemo, xrt or surg

• **GEMOX**: Gemcitabine (+cisplatin or +Oxaliplatin)
  - stomatitis, neuropathy, fatigue, neutropenia, hair loss, nausea, vomiting, sleep disturbance

• **FOLFIRINOX**: 5-Fluoruracil, Oxaliplatin, Leucovorin, Irinotecan
  - stomatitisis, neuropathy, diarrhea, nausea, vomiting, hair loss, fatigue, sleep disturbance
  - 83% of patients discontinue or have interrupted treatment due to side effects

• **GTX**: Gemcitabine, docetaxel, capecitabine
  - stomatitis, mucositis, fatigue, neuropathy, neutropenia, darkening of the palms, soles & nails,
  peeling of the skin with cracks and fissures, skin rash, sleep disturbance

NATUROPATHIC EVALUATION
WHERE TO BEGIN?

• **Look at NCCN.org and understand staging & treatment options the patient will face**
  - This allows for supportive and educational conversations with the patient AND for best collaboration with other providers


• **Get full medical history** including: records, treatment, imaging and labs

• **Interpret patency and functional status of the GI tube, Panc, Liv, GB, vessels.**
  Imaging and surgical reports may identify clear fat plane vs. involvement of great vessels, possible lesions in the liver. Keep a watch on liver function tests over time.

• **Assess the ability of the individual for intake of solids and liquids**-listen to as much as the patient can tell you about their current digestive health; create a visit habit of talking about what and how much foods are eaten and how the patient feels after eating. Use one of the validated quality of life tools for symptoms assessment.

• **Appreciate the vis – aside from all the records and diagnosis who is the person? How do they experience their symptoms, their disease, their health?**

• **Collaborate with the patients’ other providers – on interventions you initiate etc.**
**THINGS TO CONSIDER**

**Fear, vulnerability, confusion.** Patients and their families are in a whirlwind trying to move quickly after diagnosis.
- Patients are often told they don’t have much time to live.
- Patients feel at the mercy of standard treatments; out of control; as if they have nothing to lose by trying “anything” or doing nothing. Clinical environments can seem harsh.

These patients deserve efficient management & support of digestive health first & foremost on arrival to ND.
- Welcome discussion with caregivers present; most patients need a support network that can help with food prep & supp/meds schedule

**Plan for weekly visits if possible. Refer to nutritionist.**
- Keep visits 1 hour or less.

**Do not overload with pill or capsule supplements. Nutrition & digestive support are critical elements to begin in steps.**
**“PANCREATIC CANCER IS ASSOCIATED WITH DISEASE-RELATED COMPLICATIONS”**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>• Majority of patients have pain at the time of the diagnosis</td>
</tr>
<tr>
<td>Pancreatic Exocrine Insufficiency (PEI)</td>
<td>• Occurs in 80%-90% of patients; gas bloating, steatorrhea, diarrhea, malabsorption, vitamin deficiency, weight loss</td>
</tr>
<tr>
<td>Malignant Biliary Obstruction</td>
<td>• Occurs in 70%-90% of patients but is most commonly associated with pancreas head tumors; stenting common</td>
</tr>
<tr>
<td>Cancer-Associated Anorexia – Cachexia Syndrome (CACS)</td>
<td>• Observed in up to 80% of patients at the time of diagnosis</td>
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<tr>
<td>Depression</td>
<td>• More prevalent in pancreatic cancer than other types of cancer</td>
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<td>• Diagnosed in 33%-70% of patients at some point in their disease</td>
</tr>
<tr>
<td>Malignant Gastric Outlet Obstruction (GOO)</td>
<td>• Approximately 26% of patients develop GOO</td>
</tr>
<tr>
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<td>• Early satiety + pain soon after eating; less tolerant of solids</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>• Four- to seven-fold higher that other common adenocarcinomas</td>
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<tr>
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<td>• Likelihood is highest during the first 3 months after diagnosis</td>
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<tr>
<td></td>
<td>• Chemotherapy may increase the risk</td>
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LET’S SLOW THIS WHIRLWIND DOWN

• **Educate about digestive organs and physiology**
  - This is an excellent focus whereby digestion and diet are prioritized; share pictures & videos; describe functions
  - Caregivers and family are important allies to create positive focus and implement nutrition & supplement tools to aid digestion and lessen discomfort.

• **State that the pancreas is an organ of digestion and metabolic health**
  - Digestion and signaling can be interrupted by tumor and inflammation but there are some simple tools that may help so that absorption of nutrients can be improved which will provide ENERGY and decreased symptoms

• **Discuss normal vs. abnormal appetite, food intake, hydration, and bowel**
  - Most people with pancreatic cancer have been living with symptoms for some time, need the education, and it’s a good way to start discussing symptoms
PHASES OF DIGESTION

• **Luminal phase**
  Dietary fats + proteins + carbs are hydrolyzed / solubized

• **Mucosal phase**
  Brush border membrane of intestinal epithelial cells transports hydrolyzed digestive products from the lumen

• **Post absorptive phase**
  Elimination

**Pancreatic cancer disrupts luminal phase**
- downstream affects for all phases
- results in malabsorption
- inhibits absorption of macro and micronutrients
- changes fluid dynamics for hydration, increases need for electrolytes
SYNCHRONY OF DIGESTIVE PROCESSES

- **Mouth**: Salivary amylase begins breakdown of carbs
- **Stomach**: peristalsis with acid & pepsin = acidic chyme
- Mixing starts digestion of protein in presence of chyme
- **Duodenum**: Acid in chyme signals secretin & tells
  - Pancreas to produce bicarb & Liver to produce bile
  - Fat in chyme signals CCK - tells the gall bladder to release concentrated bile & pancreas to make enzymes
- Pancreatic juice: (enzymes, bicarb, protease) flows into duodenum, neutralizes acidic chyme
- Bile & bicarb activate enzymes
- Enzymes assist in breakdown of fats and proteins
PANCREAS & DUODENUM CROSSTALK: ENTEROENDOCRINE CELLS

Presence of acid in chyme stimulates cells at duodenum to produce secretin

**Secretin**
+ pancreas to produce bicarbonate
+ liver to yield bile
- Gastrin (inhibits HCl)
- gastric mobility
+ CCK

Presence of fat, aminos, and chyme in stimulates duodenum to produce CCK

**Cholecystokinin (CCK)**
+ gall bladder contraction
+ pancreatic juice & flow
+ pancreatic enzymes
- gastric mobility & secretion
+ somatostatin release

Pancreatic juice = pH ≈ 8 containing electrolytes, HCO$_3^-$, protease, enzymes
# Pancreatic Proenzymes & Enzymes

<table>
<thead>
<tr>
<th>PROENZYMES</th>
<th>ENZYMES</th>
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<tbody>
<tr>
<td>Trypsinogens (1, 2, 3)</td>
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<tr>
<td>Chymotrypsinogen (A, B)</td>
<td>α-Amylase</td>
</tr>
<tr>
<td>Procarboxypeptidase A (1, 2)</td>
<td>Lipase</td>
</tr>
<tr>
<td>Procarboxypeptidase B (1, 2)</td>
<td>DNase</td>
</tr>
<tr>
<td>Prophospholipase (I, II)</td>
<td>RNase</td>
</tr>
<tr>
<td>Proelastase</td>
<td></td>
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<tr>
<td>Mesotrypsin</td>
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Pandol SJ. The Exocrine Pancreas.  
ASYNCHRONY OF DIGESTIVE PROCESS IN PANCREATIC CANCER

- **Gastric emptying is not met with coordinated pancreatic secretion in the small intestinal lumen**
  - Failure of signaling by CCK to produce more enzymes
  - Pancreatic inflammation, tumor overrides normal cells & inhibits production of enzymes
  - Failure of signaling by secretin to result in flow of water and ions (bicarb) from pancreas

- **Improper or failure of mixing of chyme/nutrients, enzymes and bile**
  - If pancreatic juice not present, chyme is not neutralized and enzymes not activated

- **Changes in gastric and duodenal acidity**
  - Failure of HCO3⁻ in pancreatic juice to reach the duodenum
  - Gastric acid (that does not get neutralized) damages intestinal mucosa /overwhelms Brunner’s glands
  - Acid denatures enzymes, renders inactive
  - Standard protocols recommend PPI for patients to support reduction in symptoms and facilitate any amount of activity from existing enzymes via decreased acidity
  - Gastric hypersecretion more common after small intestinal surgery hence PPI protocol

- **After surgery, ie. Roux-en-Y anastomosis or pancreatic-duodenectomy, malabsorption may develop due asynchrony and bacterial overgrowth, results in inc GLP-1 & PYY (↑diarrhea & ↑anorexia)**


THE DUODENUM

• Entero-endocrine cells secrete: secretin & CCK

• Brunner’s glands secrete mucous to protect mucosa in response to intermittent pulses of gastric H+ / chyme (pH 3-4)

• Regulates the digestion of fats and proteins

• Regulates the emptying of the stomach via hormones

• Thought to be a primary absorptive site for iron

• Site of activation of pancreatic enzymes (pH 5-6) & initial hydrolysis of fats, proteins, carbohydrates

• Primary pancreatic surgeries performed to preserve duodenum
SYMPTOMS THAT MAY HERALD DIAGNOSIS

weight loss, diarrhea, abdominal pain, post prandial symptoms, fatigue, gas & bloating, jaundice, early satiety, pale stools, floating stools


- Exocrine pancreatic insufficiency (EPI)
  - May be present in 90% of patients diagnosed with panc cancer, 50% of patients with cystic fibrosis, 35% of patients with type II diabetes, 20% of patients with irritable bowel disease

EXOCRINE PANCREATIC INSUFFICIENCY (EPI)

Symptoms indicating <10% of pancreatic function in panc ca:
- post prandial discomfort/pain
- gas/bloating
- steatorrhea
- diarrhea

One of the earliest manifestations of EPI is thought to be decreased bicarbinate secretion associated with post prandial gas/bloating.

Diagnosis:
- May be diagnosed on suspicion or tested ie. fecal elastase test (90% specific 72% sensitive)
- In pancreatic cancer dx of EPI is presumptive; Tx is PERT
- PERT: Pancreatic Enzyme Replacement Therapy

Sikkens 2014
PANCREATIC INSUFFICIENCY TESTS
-NOT GENERALLY USED TO DX EPI IN PANC CA

- **Amylase** – blood, urine, peritoneal fluid; monitor & dx chronic pancreatitis (4-6x’s normal); run with lipase to assess for pancreatic duct obstruction
- **Fecal Fat** – chronic diarrhea/steatorrhea to confirm malabsorption; if qualitative neg, do 72 hour quant
- **Lipase** – abdominal pain, fever, anorexia, nausea, elevated in alcoholic pancreatitis; duct obstruction
- **Trypsin/Chymotrypsin** - test panc insuff in CF
- **Fecal elastase**- is a protein cleaving enz; markedly decreased in panc insuff
- **Mixed triglyceride breath test**
- **CCK Secretin test**
- **Visual stool examination** – greasy, pale, floating
INSTEAD OF TESTS, ASK QU’S

• Do stools float?
• Is there a grease or oil in the toilet bowl?
• Post prandial sx? (abdominal pain, gas bloating, diarr)
• Diarrhea? How often, how many times per day?

• Yes to these generally indicate fat malabsorption with pancreatic exocrine insufficiency.
• Consider some patients don’t talk about diarrhea easily.
• Note any improvement via frequent check-ins after interventions such as enzymes, probiotics, nutrition & dietary changes.
SYMPTOMS & CONVENTIONAL ADVICE

Symptom & conventional advice:

Cachexia- eat everything you can tolerate, keep weight up, don’t skip meals
Problem: patients drastically self-limit intake and variety of nutrients; fatigue worsens; patients feel like they failed

Diarrhea- anti-diarrheals, avoid fatty foods, try pancreatic enzymes with meals; titrate up in dose; if no effect- bile sequestrant
Problem: not enough education about how and why or what to watch for; lack of patient support in how to take enzymes

Gas, bloating- simethicone, avoid fatty foods, consume small meals frequently

Anorexia-appetite stimulant (megastrol), marinol

Pain control – narcotics, radiation, celiac plexus nerve block
-supplements probably won’t help
-drink meal supplement beverages

THERE’S SO MUCH POTENTIAL TO IMPROVE ON THIS!

NATUROPATHIC IDEAS

- **Improve digestion** – add enzymes, liberalize nutritious intake
- **Reduce pain** – improve digestion function/support symptoms, natural anti-inflammatories, castor oil pack, massage, acupuncture, advocate for pain management, eliminate contributing factors in diet/lifestyle
- **Decrease inflammation** – Curcumin, Boswellia, IVC, Delta Gamma Tocotrienols
- **Improve sleep** – advocate for regulation of night & day sleep cycle; keep all daytime naps to under 1 hour; get daylight in the eyes during the day; supplemental melatonin; sleep hygiene
- **Reduce Stress** / Promote calm, breathing, relaxing movement, visualization, following interests/joys, time with loved ones
- **Intensive nutrition counseling** Stabilize weight
- **Improve quality of life** – manage digestive symptoms with functional, practical approach; consider weekly or twice weekly IVC
WHAT ARE PANCREATIC ENZYMES?

Formulas of lipase, protease and amylase enzymes from fungal, plant or porcine sources; microspheres in enteric capsules; activity is correlated with lipase content ("pancrelipase") but also may contain other digestive aids such as DGL, althea, gamma oryzanol. Drug development for engineering human enzymes is underway.

• **Studies report benefit in cystic fibrosis, pancreatitis, pancreatic cancer & surgery**¹

• **EPI patients have shorter fed patterns and faster intestinal transit that can be slowed/reversed with enzyme therapy**¹

• **Several studies report benefit (reduction in symptoms & weight loss) with enteric coated bicarbonate + enzymes** prior to titration of enzyme total dose²-⁵

• **Most common patient report after enzyme use: I feel better after eating.**

ENZYME DOSING
START WITH LOW INCREMENT OF TOTAL MEAL DOSE

Initial dosage lipase based enzymes, is a total meal dose:
• 500-1000 units lipase/kg bodyweight per meal (up to 2500 units/kg/meal)
• For people 100lbs to 220lbs this is 24,000-72,000 unit minimum dose/meal

Ex.100lbs= min dose:24,000 IU/ meal, max dose 100,000 IU/meal
150lbs= min dose: 36,000IU/meal, max dose 170,000 IU/meal
(I have never seen someone make use of more than 100,000IU/meal)

Decide on initial dose, then divide by 3-4 to get unit dose
Ex. 36,000 per meal dose /3 = 12,000 unit dose – patient will take 1 three times throughout meal

Advocate for enzyme use with snacks
• 5,000-25,000 IU per snack or ½ of total meal dose (1 during, 1 at the end)

Upper limit dosing: 2,500 units lipase/ kg bodyweight per meal
• Do not exceed 10,000 IU lipase /kg bodyweight per day

For a sufficient script consider needs for 3-4 meals and 2-3 snacks per day.
• Note range of incremental doses available
• Note size of capsules
• Plan total dose per meal & divide for 3-4 capsules to be taken throughout meal
• Prescriptions & co-pays can be expensive & OTC products are cheap and may be effective but may require more capsules per dose for efficacy.

ENZYMES:  
CONSIDER DOSING BY SYMPTOM SEVERITY & MIMIC SYNCHRONY

If post prandial gas and bloating, no diarrhea:  try OTC nutraceutical enzymes spaced as 1 capsule taken 3-4 times throughout a meal and 1-2 with all snacks.

If post prandial gas, bloating and some diarrhea with some normal bowel movements:
- start with scripts for lipase based enzyme: 12,000 unit caps taken as 1-3 per meal and continue 1-2 OTC enzyme at end of meal
- some patients prefer to double up on/continue with OTC enzymes as symptoms increase and use only 1 lipase based prescription enzyme per meal and at a time when symptoms increase eventually may use more

Overall, try smaller units lipase and dose 2-4 capsules throughout meals instead of 1 giant cap
If total dose 36,000 units per meal, have patient take (3) 12,000 unit caps throughout the meal
What Else?

Some patients report feeling better with enzymes not realizing they were challenged prior (symptom status quo x years?), may see weight & energy level ↑

Adjust dose/titrates up to maximal benefit per patient report in the short run; patients may get to a plateau period where they’re consuming more liberal diet, have stable weight, increased energy; this is great

If initial trial of enzymes is helpful and some symptoms persist, but increased enz dose aren’t helpful, try enteric coated bicarbonate 325mg /650mg taken prior to the meal

-Educate on diet and plan for future care prior to worsening symptoms occurring

-Additional supportive: probiotics bid, fat sol vits, nutrition education, planning

Gotteland M, Brunser O, Bruchet S. Systematic Review: are probiotics useful in controlling gastric colonization by helicobacter pylori?


IF PERSISTENT DIARRHEA WITH THE ABILITY TO CONSUME FOOD

If post prandial-diarrhea like clockwork

-start with 36,000 per meal dose given in 6,000-12,000 IU per capsule to take 4-5 per meal “take a few bites then enzyme, then a few bites, then another enzyme”

-symptom check at 1 week

-if improved, increase by one 12,000 unit dose per meal and have patient note whether further benefit

-consider addition of enteric bicarbonate pre-meal
ENZYME DOSE SCHEDULE & MODIFICATION
- CONSIDER ENTERIC SODIUM BICARBONATE

**Dose escalation:** enz dose may be titrated up to achieve symptom relief per patient report of: diarrhea, gas & bloating, post prandial pain; **beyond 36,000/meal is not associated w/further benefit**

Some studies report an alternative prior to/ if no benefit in titrating:

- **smaller doses taken at intervals throughout a meal may have inc benefit**¹ le. 12,000 IU x 3-4 caps pancreatic lipase throughout a meal (total dose 36,000 IU)
  *advantages: smaller capsules, possibly simulates synchrony of digestion with pulsed delivery

- **enteric bicarbonate prior to meals may improve efficacy of enzymes**²
  *advantage: significantly decreased fat excretion reported in sev studies
  *Use of enteric bicarb may help ensure enzyme activation in duod
  * 325mg or 650 mg taken prior to meal

“The goal of pancreatic enzyme therapy is to restore fat absorption by delivering a sufficient amount of active lipase at the right place, i.e., duodenum and proximal jejunum, and at the right time, i.e. in parallel with gastric emptying of nutrients”


CACHEXIA & ORAL NUTRITION

Start enzymes prior to diet modification and Begin diet/nutrition education on 1st visit
- enzymes allow better tolerance of a liberal diet

Diet Modification:
• **30-35% of calories should come from fat, provide handouts w/food choices & servings**
  - supports weight stabilization associated w/ survival & QoL
• **Prioritize nutrient rich foods; plant based; protein, complex carbs**
  - nut butters, hummus, olives, yogurt, avocado
• **↑/add Medium Chain Triglycerides**
  - may be more easily absorbed in small intestine
  - food sources: coconut oil/milk, manufactured “food enhancers”
• **↑Soluble/insol fiber foods**
  - oats, applesauce, banana, whole cooked veg/fruit (↑bioavail, easier to digest, less irritation to mucosa), consider use of pectin or arabinogalactan daily for diarrhea control
• **As volume of food ↓, calorie & nutrient density should ↑ bite for bite, small freq meals**
• **Hydration is critical:** eliminate alcohol, sugared beverages, champion pure water intake; strategize between meal hydration to meet goals.
• **Consider nutrient /supplement meal beverages as snacks and additional to meals**

FAT SOLUBLE VITAMINS
- PROBABLE DEFICIENCY

- **Consequences of abnormal lipid digestion:**
  - malnutrition (fatigue, weight loss)
  - depletion of lipid-soluble vitamins & associated sx’s
  - depleted micronutrients & and associated fallout
  - decreased circulating lipoproteins

- **Prioritize supplementing:**
  - vitamin A, D, E, K, selenium, zinc, B12, calcium, iron
  - use of PPI’s associated with inhibited absorption zinc, B12

Patients with symptoms of fat malabsorption who experience benefit from enzymes are also reported to replete deficiencies when supplemented.¹⁻⁴

PROBIOTICS

• ↓ infxs complications after pancreaticoduodenectomy PMID:17591036
• ↓ gastric inflammation
• ↓ apoptosis
• ↓ bacterial overgrowth
• Stabilize intestinal barrier (junction proteins, cell polarization)
• ↑ secretion of protective mucins & defensins
• Evidence supports use in gastroenteritis conditions
• ↓ PPI-associated bacterial colonization of colon
• May reduce bowel side effects of chemo
• Consider 2-3 times daily dosing between meals

Gotteland M, Brunser O, Bruchet S. Systematic Review: are probiotics useful in controlling gastric colonization by helicobacter pylori?
Causes of diarrhea:
- asynchrony of luminal digestion
- endogenous bile salts delivered profusely to duod
- lack of lipase enzyme or enzymes without chyme
- mucosal inflammation due to gastric acid
- bacterial overgrowth

What’s the role of fiber? BIND BILE, bulk stool, REDUCE DIARRHEA

- Soluble dietary fibers may reduce secondary bile acid concentrations in fecal water and reduce fecal toxicity leading to diarrhea
- Alginates, pectin and natural polysaccharides occurring in agents such as arabinogalactan, ulmus, althea may be bioadhesive for bile, mucoprotective, support gastric emptying and decrease bile reflux
- Luminal agents: opiate analogues, bile acid sequestrants, probiotics, bismuth compounds, berberine, bupleurum
- Example of helpful dosing: 1T. Arabinogalactan powder in water tid or 3-4 pectin capsules tid

LUMINAL ACTING ANTI-DIARRHEAL AGENTS
MENEES, S. ET AL. (2012) AGENTS THAT ACT LUMINALY TO TREAT DIARRHOEA AND CONSTIPATION NAT. REV. GASTROENTEROL. HEPATOL. DOI:10.1038/NRGASTRO.2012.162

<table>
<thead>
<tr>
<th>Agent category</th>
<th>Mechanism of action</th>
<th>Clinical considerations</th>
</tr>
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<tbody>
<tr>
<td><strong>Currently available agents</strong></td>
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</tr>
<tr>
<td>Opioids e.g. loperamide</td>
<td>Binds to opioid µ receptors; increases nonpropulsive contractions; decreases longitudinal propulsive peristalsis; leads to increased contact time for absorption</td>
<td>Acute and chronic diarrhea; improves diarrhea but perhaps not pain in IBS-D; preferred for chronic treatment as it has less potential for dependence</td>
</tr>
<tr>
<td>Bile acid sequestrants e.g. cholestyramine, colesevelam, colestipol</td>
<td>Reduces colonic bile acids that cause increased intestinal secretion, increased mucosal permeability and acceleration of colonic transit</td>
<td>Best suited for bile-acid-related diarrhea; colesevelam and colestipol available in tablet form; can interfere with absorption of other medications</td>
</tr>
<tr>
<td>Antibiotics e.g. rifaximin</td>
<td>Alters gut microbiota</td>
<td>Effective for traveller’s diarrhea prophylaxis and nonconstipated IBS</td>
</tr>
<tr>
<td>Probiotics e.g. various single and combination probiotic preparations</td>
<td>Blocks production of microbial toxins; inhibits pathogen adhesion; stimulates the immune system; restricts colonization resistance</td>
<td>Effective for acute infectious diarrhea and IBS; strain-specific effects; no long-term efficacy or safety data; quality control issues (regulated as food additives not drugs)</td>
</tr>
<tr>
<td>Bismuth subsalicylate e.g. Pepto-Bismol®</td>
<td>Antimicrobial, antitoxin and anti-inflammatory actions</td>
<td>Effective for prophylaxis and treatment of traveller’s diarrhea, acute diarrhea, and microscopic colitis; avoid in patients with renal insufficiency</td>
</tr>
<tr>
<td>Berberine</td>
<td>Bactericidal activity; decreases enterotoxin-induced intestinal secretion of water and electrolytes; inhibits protozoan growth</td>
<td>Poor quality evidence for bacterial gastroenteritis, giardia infection and acute radiation-induced diarrhea; quality control issues (regulated as food supplement not a drug); most appropriate dose for diarrhea unknown</td>
</tr>
<tr>
<td><strong>Emerging agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enkephalinase inhibitors e.g. rasedotril (also known as acetorphan)</td>
<td>Reduced degradation of enkephalin by enkephalinase leads to increased binding of δ receptors and inhibition of adenylate cyclase resulting in potent absorptive and antisecretory effects</td>
<td>Approved for the treatment of acute diarrhea in Europe; not available in the USA</td>
</tr>
<tr>
<td>Adsorbant natural clay e.g. diosmetcite</td>
<td>Adsorption of toxins, bacteria and viruses; reinforcement of the intestinal mucus barrier reducing penetration of luminal antigens; modulating production and effects of proinflammatory cytokines</td>
<td>Grade IIB recommendation by European societies for the use of acute gastroenteritis; not available in the USA</td>
</tr>
<tr>
<td>Chloride channel inhibitors e.g. crotelmer</td>
<td>Inhibits two distinct chloride channels (CFTR and CIC-2) found on the apical surface of enterocytes</td>
<td>Undergoing priority review by the FDA for HIV-induced diarrhea; benefits for pain in women with IBS-D in a phase II study</td>
</tr>
</tbody>
</table>
Integrative treatment of digestive symptoms in Pancreatic Cancer

Wasting, extreme fatigue, diarrhea, ECOG 4

Symptoms
- Gas & Bloating
- Steatorrhea
- Diarrhea
- Weight loss
- Persistent weight loss and fatigue

WITH OR WITHOUT:
- Abdominal pain
- GERD - Fatigue
- Nausea

Interventions
- Bicarb or PPI
- Probiotics
- Marinol
- MCT
- High lipase enzyme
- Vitamins/ minerals: A,D,E,K,Zn,Ca,Fe,B12
- Cholestyramine or pectin enriched cholestyramine
- PPI
- Anti-diarrheal such as luminal acting opiate
- Diet modification (reduce fat as tolerated)

Symptoms
- Gas & Bloating
- Steatorrhea
- Diarrhea
- Weight loss

WITH OR WITHOUT:
- Abdominal pain
- GERD - Fatigue
- Nausea

Interventions
- Bicarb or PPI
- Probiotics
- Marinol
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Symptoms
- Gas & Bloating
- Steatorrhea
- Diarrhea

WITH OR WITHOUT:
- Abdominal pain
- GERD - Fatigue
- Nausea

Interventions
- Bicarb or PPI
- Probiotics
- Marinol
- MCT
- High lipase enzyme
- Vitamins/ minerals: A,D,E,K,Zn,Ca,Fe,B12
- Pectin or soluble polysaccharide fiber

Symptoms
- Gas & Bloating
- Steatorrhea

WITH OR WITHOUT:
- Abdominal pain
- GERD - Fatigue
- Nausea

Interventions
- Bicarb or PPI
- Probiotics
- Marinol
- MCT
- High lipase enzyme
- Vitamins/ minerals: A,D,E,K,Zn,Ca,Fe,B12

Symptoms
- Gas & Bloating

WITH OR WITHOUT:
- Abdominal pain
- GERD - Fatigue
- Nausea

Interventions
- Enteric Bicarbonate 325mg or 650mg bid OR PPI
- Probiotics
- Marinol as anti-emetic
- D3
- Food sources of medium chain triglycerides (MCT)

Patient usually presents at this tier of intervention after partial or total pancreatectomy.
TOOLS FOR ASSESSING POTENTIAL EFFICACY OF INTERVENTIONS

- Pancreatic cancer presents challenges to any assessment of efficacy for any intervention due to its quick progression as a confounding factor.
- Weekly check in’s become important
- PRO questionnaires: tools that prioritize patient reported symptoms that are most likely to interfere with quality of life
  - NCCN-FACT Hepatobiliary-Pancreatic Symptom index
  - PACADI

TOP 5 questions: energy, pain, fatigue, weight loss, abdominal symptoms
OTHER STUFF

• Remeron, Dronabinol, Cannibis support appetite

• Mu opioid receptor antagonists

• Castor oil packs can be helpful for liver/abd pain

• Melatonin 20mg hs has impressive supportive data in digestive tract cancers including pancreatic

• Homeopathics are GREAT for helping painful symptoms: gas & bloating, nausea & patients happy not to swallow another pill

• Constipation: hydrating enema, senakot –s, increase water intake to optimal, smooth move tea, cold pressed sesame oil (PMID:22544841)
NATUROPATHIC AGENTS THAT MAY FIGHT PANCREATIC CANCER

- **Sulforaphane**

- **Delta Gamma tocotrienol**
  PMID: 23302291, 20864511

- **Curcumin**
  Phase III Trial of Gemcitabine, Curcumin and Celebrex in patients with advanced or inoperable pancreatic cancer [Tel-Aviv Sourasky Medical Center] ClinicalTrials.gov  NCT#: 00486460

- **Melatonin**

- **Cannabinoids**

- **Viscum**

- **Thymoquinone Augments Chemotherapy Treatment of Pancreatic Cancer by Jacob Schor, ND FABNO**

- Euvascular
- Patent vessels
- Functionally/structurally intact vessels
- IFP low

- Hypervascular
- Patent vessels
- 'Leaky'/structurally abnormal vessels
- IFP moderate

- Hypovascular
- Collapsed vessels
- Structurally intact vessels
- IFP high
VITAMIN C MAY HELP ADDRESS THE STROMA

- Vitamin C is anti-inflammatory and may take part in stromal activity to decrease the hospitality of the stroma to the malignant entity.
  
  Clementz AG, Harris A. Collagen XV: exploring its structure and role within the tumor microenvironment. Mol Cancer Res. 2013;11(12):1481-6

- Vitamin C could be considered for potential activity in the tumor microenvironment, which contains inflammatory proteins such as VEGF, IL-8, and other cytokines that favor malignant processes.
  
  

- IVC
- Deep tissue hyperthermia
IVC Clinical Study Protocol Summary

Title: Evaluation of the safety and efficacy of standard dose Gemcitabine combined with high dose intravenous Vitamin C (HDIVC) treatment for patients with metastatic adenocarcinoma of the pancreas.

Objectives:
Primary Establish safety of standard dose Gemcitabine in combination with HDIVC
Secondary Compare progression-free survival (PFS) in patients receiving Gemcitabine + HDIVC with the PFS (RECIST criteria*) of the most recent therapy on which the patient has experienced progression1,2

Other measurements to be reviewed:
• Monitor CA 19-9 every four weeks
• Assess Quality of Life (QOL) with EORTC questionnaire**
• Monitor inflammatory markers: CRP, ESR, Ferritin
• Monitor blood plasma ascorbic acid levels

Safety and tolerability, Progression-free survival, Adverse Events. (Measurements of tumor markers, quality of life, Vitamin C plasma levels, and inflammatory markers do not pose additional risks to the patient and will be reviewed for any encouraging trend.)

Study Subjects: 10 patients with biopsy proven metastatic adenocarcinoma of the pancreas who have experienced disease progression after at least one prior treatment regimen.

Study Design: Prospective single-arm trial conducted in two part enrollment with 3 patients evaluated for safety prior to further accrual of another 7 patients.

Study Drugs: Gemcitabine (XXX), Intravenous and oral Ascorbic Acid (Vitamin C).
Dosage and Treatment Schedule: (Weeks 1-4: represents 1 cycle)
• Weeks 1,2,3: IV Gemcitabine 1000 mg / m2 over 30 minutes followed by HDIVC 1.2 g / kg over 90 minutes followed by 0.3 g / kg over 120 minutes; Week 4: no treatment.

* Response Evaluation Criteria in Solid Tumor
** The European Organisation for Research and Treatment of Cancer
PHASE I PROTOCOL: EVALUATION OF THE SAFETY AND EFFICACY OF STANDARD DOSE GEMCITABINE COMBINED WITH HIGH DOSE INTRAVENOUS VITAMIN C (HDIVC) FOR THE TREATMENT OF PATIENTS WITH METASTATIC ADENOCARCINOMA OF THE PANCREAS

H WRIGHT ND FABNO, E KLIMANT MD FACP

The treatment schedule: iv gemcitabine 1000 mg/m² administered over 30 minutes, followed by HDIVC 1.2 g/kg over 90 minutes for a dose ≤ 90 g or 1.2 g/kg over 120 minutes for a dose >90 g, followed by 0.3 g/kg over 120 minutes. Treatment given weeks 1,2,3 with treatment break on week 4 per cycle. Non-Corn IV vitamin C was used. Oral liposomal vitamin C gel was given as 2,000mg twice daily (4,000 mg total daily).

First 3 patients enrolled - case synopses:

- **Patient 1:** 53 year old female with pancreatic cancer with metastasis to the lung, mediastinum, liver, and skeleton. She underwent 1st line treatment with FOLFIRINOX, 2nd line treatment with 5 cycles of gemcitabine, docetaxel, capecitabine (GTX) and 3rd line treatment in this study. She was hospitalized after receiving 2 cycles of treatment and subsequently died.

- **Patient 2:** 52 year old male with metastatic pancreatic cancer to the liver, status post 11 cycles FOLFIRINOX followed by 2 cycles treatment on this study regimen, followed by 6 cycles of treatment on GTX with a treatment response after 3 cycles of GTX, followed by 2 chemoembolizations to the liver, followed by 8 cycles gemcitabine paclitaxel followed by 1 cycle gemcitabine and cisplatin. The patient is currently alive 3 years since diagnosis on hospice.

- **Patient 3:** 59 year old male metastatic pancreatic cancer with liver disease, status post chemoradiation therapy with weekly gemcitabine, treated subsequently with 8 cycles GTX for 1st line metastatic treatment, 2nd line was treated on this study regimen and had 3rd line treatment with 4 cycles gemcitabine and nab-paclitaxel with treatment response after 4 cycles.
HIGH DOSE IVC
FOLLOWED BY LOW DOSE IVC
CONTINUES PLASMA ELEVATION

<table>
<thead>
<tr>
<th>Patients receiving study treatment</th>
<th>Plasma vitamin C level 30 minutes after start of 1.2 g/kg dose</th>
<th>Plasma vitamin C level 30 minutes after start of 0.3 g/kg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>159.23 mg/dL</td>
<td>239.44 mg/dL</td>
</tr>
<tr>
<td>Patient 2</td>
<td>146.37 mg/dL</td>
<td>195.57 mg/dL</td>
</tr>
<tr>
<td>Patient 3</td>
<td>83.37 mg/dL</td>
<td>315.95 mg/dL</td>
</tr>
<tr>
<td></td>
<td>141.32 mg/dL</td>
<td>317.87 mg/dL</td>
</tr>
<tr>
<td></td>
<td>70.55 mg/dL</td>
<td>128.56 mg/dL</td>
</tr>
</tbody>
</table>

Could add inflamm marker levels, could discuss issues with use of port blood for study analysis – hep lock/interference. Always use contralateral extremity for draws. Discuss sendout for plasma C levels & lab issues with reporting. ID infusion or research nurses who can do the draws every time & lab personnel who will handle your samples. Become friends.
IVC USE IN HOSPITALS: A RATIONAL APPROACH

- **Present data that clearly reports on safety** and rationale for use of IVC in patients with cancer
- **Familiarize with the potential strengths and limitations** of the human studies
- Champion IVC as a potential tool in supportive care
- **Prepare a brief presentation for medical colleagues** & points of referral
- **Promote a system of safety**: provide in-service & educational meetings with infusion, pharmacy, departments & colleagues who may potentially refer order or administer IVC
- **Develop evidence based criteria for guidelines**: Indications, contraindications, precautions, possible side effects, dosing
RATIONALE:
SAFETY & BENEFIT OF IVC AS SUPPORTIVE CARE

- Phase I trials giving IVC 10-220 g to patients with cancer alone and in combination with chemotherapy report safety and tolerability, reduction in symptoms & improved quality of life.
GUIDELINE ELEMENTS FOR HOSPITAL BASED IVC TREATMENT

Indications:
• Presumptive vitamin C deficiency or depletion along with: fatigue, anemia of chronic disease, reduced oral intake, history of surgery or radiation to areas of the GI tract, history of malabsorption, treatment with chemotherapy having intestinal or mucosal side effects, slow wound healing or infection.
• Symptoms of: fatigue, muscle weakness, arthralgia, myalgia, neuropathy, bleeding gums, poor wound healing, lower extremity edema, poor oral intake, loss of appetite, pain and depression.

Contraindications:
• Glucose-6-phosphate dehydrogenase deficiency (G6PD normal: 4.6-13.5 U/g Hgb)
• Uncontrolled serum glucose >300 mg / dL (16.7 mMol)

Precautions:
• Renal insufficiency: IVC may given at the discretion of the provider if Creatinine >2.0
• Hypercalcemia or oxaluria: IVC may given at the discretion of the provider.
• Metal storage diseases: Hemochromatosis or Wilson’s disease. Regular monitoring is recommended.
• Iron overload due to frequent transfusion history.
• Caution during adjuvant therapy with curative intent due to limited data on treatment efficacy.

Possible Side Effects:
• Finger stick glucose monitoring may be abnormal for 1-6 hours after IVC.
• Side effects previously reported in clinical trials providing have included: nausea, dizziness, dry mouth, fatigue, perspiration and weakness. These are not likely with doses of IVC < 30 g however caution is advised.

Frequency & Duration of IV & Oral Vitamin C:
• IVC may be given 1-3 times at the discretion of the provider.
• Recommended dosing for oral vitamin C during and after IVC may be given at the discretion of the provider.
KEY POINTS TO CONSIDER WITH USE OF IVC IN ONCOLOGY PATIENTS

- Test each patient for G6PD deficiency (quantitative & total RBC) prior to IVC treatment.
- Do not give IVC to G6PD deficient patients. Check for recent history of hemolysis and transfusion (could mask deficiency) and if present, retest for G6PD within 8-12 weeks.
- Use caution when giving high gram doses of oral vitamin C - know the G6PD status of patients.
- IVC is rapidly excreted via the renal system and thus requires adequate kidney function. Use caution when giving high dose IVC (ie. >25-30 g) to patients with a history of kidney stones or oxaluria.
- IVC could be given prior to chemotherapy followed by a break depending on the dose of IVC to allow for clearance and avoid any significant interaction with chemotherapy.
- IVC may be given after chemotherapy per the discretion of provider depending on chemotherapy metabolism and clearance time i.e. 12-72 hours after chemotherapy.
- IVC may be given 30-60 minutes prior to IV iron at the discretion of the provider.
- IVC can be administered through an in-dwelling venous access system or port.
- Encourage oral hydration during and after infusion.
- Do not administer IVC within 12-24 hours prior to PET scan.
- Caution for use of IVC during adjuvant therapy with a curative intent as there is limited data on the effect of IVC on treatment efficacy.
- Ascorbate for intravenous administration is combined with sterile water prior to administration. We do not have published human data reporting on additives to IVC at this point.
- As ascorbate in solution may degrade with light exposure, a bag drape is recommended.
## SAMPLE DOSING

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Nutrient</th>
<th>Osmolarity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Water</td>
<td>IVC g</td>
<td>m/L</td>
<td>Minutes</td>
</tr>
<tr>
<td>100mL</td>
<td>3g</td>
<td>336</td>
<td>30</td>
</tr>
<tr>
<td>150mL</td>
<td>6g</td>
<td>440</td>
<td>30 60</td>
</tr>
<tr>
<td>250mL 300mL</td>
<td>10g</td>
<td>440 371</td>
<td>60 90</td>
</tr>
<tr>
<td>200mL 250mL</td>
<td>12g</td>
<td>636 440</td>
<td>60 90</td>
</tr>
<tr>
<td>250mL 350mL</td>
<td>15g</td>
<td>636 469</td>
<td>60 90</td>
</tr>
<tr>
<td>500mL</td>
<td>20g</td>
<td>440</td>
<td>90 120</td>
</tr>
<tr>
<td>500mL 750mL</td>
<td>25g</td>
<td>371 540</td>
<td>90 120</td>
</tr>
<tr>
<td>750mL</td>
<td>30g</td>
<td>440</td>
<td>90 120</td>
</tr>
<tr>
<td>750mL</td>
<td>50g</td>
<td>698</td>
<td>120 180</td>
</tr>
<tr>
<td>1000mL</td>
<td>75g</td>
<td>774</td>
<td>120 180  240</td>
</tr>
</tbody>
</table>
WHAT’S THE SOLUTION- NOW & FUTURE?

• Whole exome sequencing, intensive surveillance and early detection and removal with continued search for targeted therapies?

• What about gene influencing and culture specific risk factors under the pressure of every day selection in terms of diet and physical activity as well as exposures?

**Maximal support for QoL & effective symptom management** through use of combined integrative and standard care therapies

**Public education to support awareness of & reduction in known risk factors**
nutrition, digestion, metabolic health, weight, exercise, exposure

**Increasing public & clinical education on early signs & symptoms**
-potential early diagnostic markers for disease such as CCK

**Clinical trials to test practical, integrative tools for symptom management and QoL**
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Gross appearance</th>
<th>Key features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinar cell carcinoma</td>
<td>Solid</td>
<td>Rare, exocrine enzyme production, aggressive</td>
</tr>
<tr>
<td>Adenocarcinoma (ductal)</td>
<td>Solid</td>
<td>Common, haphazard arrangement of neoplastic glands, cytokeratin 7 and 19 production, highly aggressive</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td>Cystic</td>
<td>Common, arise in the ducts, produce luminal mucin, may progress to invasive carcinoma</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm (MCN)</td>
<td>Cystic</td>
<td>More common in women, columnar, mucin-producing, ovarian stroma, may progress to invasive</td>
</tr>
<tr>
<td>Pancreatic intraepithelial neoplasia (PanIN)</td>
<td>Microscopic</td>
<td>Arise in smaller pancreatic ducts, ductal differentiation, precursor to invasive carcinoma</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor (PanNET)</td>
<td>Solid</td>
<td>Uniform cells grow in sheets, salt-and-pepper nuclei, neuroendocrine differentiation with expression of synaptophysin and chromagranin, less aggressive than ductal</td>
</tr>
<tr>
<td>Serous cystadenoma (SCN)</td>
<td>Cystic</td>
<td>Central star shaped scar, cuboidal glycogen rich cells, majority benign</td>
</tr>
<tr>
<td>Solid-pseudopapillary neoplasm (SPN)</td>
<td>Solid and cystic</td>
<td>More common in women, express CD10&amp;CD99, 10% are aggressive</td>
</tr>
</tbody>
</table>
### INHERITED SUSCEPTIBILITY

<table>
<thead>
<tr>
<th>Genetic Mutations</th>
<th>Syndrome</th>
<th>Lifetime risk</th>
</tr>
</thead>
</table>
| BRCA1, BRCA2      | Hereditary breast/ovarian cancer syndrome | • BRCA2 mutation is the most common known familial genetic cause  
• 3.6%-5% lifetime risk |
| PALB2             | PALB2 is the molecular adaptor between the BRCA proteins. Impaired homologous recombination repair is one of the fundamental causes for genomic instability and tumorigenesis observed in patients carrying BRCA1, BRCA2, or PALB2 mutations. Individuals with two PALB2 mutations have a type of Fanconi anemia which is associated with additional cancer risks. | • 3% of patients with familial pancreatic cancer  
• Lifetime risk is not well defined  
• Increased risk of breast cancer, acute myeloid leukemia (AML), tumors of the head, neck, skin, gastrointestinal system, or genital tract. The likelihood of developing one of these cancers in people with Fanconi anemia is 10-30% |
| P16/CDKN2A        | Familial atypical multiple-mole melanoma | • 10%-17% lifetime risk for pancreatic cancer |
| STK11/LKB1        | Peutz-Jeghers syndrome | • 11%-36% lifetime risk for pancreatic cancer |
| PRSS1             | Hereditary pancreatitis | 25%-40% lifetime risk for pancreatic cancer |
| MLH1, MSH2, MSH6, PMS2 | Hereditary non-polyposis colon cancer (Lynch syndrome) | 3.7% lifetime risk for pancreatic cancer |

STAGING OF PANCREATIC CANCER

- T1, T2, and T3 tumors are potentially resectable
- T4 which involve the superior mesenteric artery or celiac axis, are unresectable

### Staging of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Grade</th>
<th>Nodal Status</th>
<th>Distant Metastases</th>
<th>Medial Survival (MO)</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| IA    | T1          | N0           | M0                 | 24.1                | • Tumor limited to the pancreas  
  • ≤2 cm in longest dimension |
| IB    | T2          | N0           | M0                 | 20.6                | • Tumor limited to the pancreas  
  • >2 cm in longest dimension |
| IIA   | T3          | N0           | M0                 | 15.4                | • Tumor extends beyond the pancreas but does not involve the axis or superior mesenteric artery |
| IIB   | T1, T2, or T3 | N1           | M0                 | 12.7                | • Regional lymph-node metastasis |
| III   | T4          | N0 or N1     | M0                 | 10.6                | • Tumor involves the celiac axis or the superior mesenteric artery |
| IV    | T1, T2, T3, T4 | N0 or N1     | M1                 | 4.5                 | • Distant metastasis |

- N denotes regional lymph nodes, M distant metastases, and T primary tumor

PATHWAYS GENETICALLY TARGETED IN THE MAJORITY OF PANCREATIC CANCERS

- Apoptosis
- DNA damage control
- Regulation of G₁–S phase transition
- Hedgehog signaling
- Homophilic cell adhesion
- Integrin signaling
- c-jun N-terminal kinase signaling
- KRAS signaling
- Regulation of invasion
- Small GTPase–dependent signaling (other than KRAS)
- TGF-β signaling
- Wnt/Notch signaling