

Perspectives on Pancreatic Cancer

Internal Medicine Grand Rounds
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Sanford Health
9 December 2015



Objectives

- Review treatment and outcomes for various stages of pancreatic cancer
- Outline evidence supporting neoadjuvant approaches to pancreatic cancer
- Discuss a patient's perspective on pancreatic cancer



Pancreatic cancer

- "Pancreatic cancer" = adenocarcinoma
- 11th most common cancer diagnosis in 2014¹
 - 48,960 cases last year
- 4th most common cause of cancer death in US
 - 40,560 deaths last year
- 5 year overall survival: 6.7%

¹American Cancer Society, Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015.



Treatment of pancreatic cancer

- The path to cure goes through surgery
- "Practical" staging system
 - Potentially resectable 20%
 - Locally advanced/borderline resectable \rightarrow 30%
 - Locally advanced/unresectable
 - Metastatic 50%



Treatment of metastatic pancreatic cancer

- Gemcitabine¹
 - Response rate: 5-11%
 - "Clinical benefit" response rate: 25-30%
 - Overall survival: 5.6 mo (vs 4.4 mo with placebo)
- Gemcitabine/nab-paclitaxel (Abraxane)²
 - Response rate: 23% (vs. 7% with gemcitabine alone)
 - Overall survival: 8.5 mo (vs. 6.5 mo with gemcitabine alone)
- FOLFIRINOX³
 - 5-fluorouracil, irinotecan, oxaliplatin
 - Response rate: 33% (vs. 9% with gemcitabine alone)
 - Overall survival: 11.1 mo (vs. 6.7 mo with gemcitabine alone)

¹ Rothenberg ML, et al. Ann Oncol. 1996;7(4):347.

² Von Hoff DD, et al. J Clin Oncol 31, 2013 (suppl);abstr 4005).

³ Conroy T, et al. N Engl J Med. 2011;366(19):187.




Treatment of metastatic pancreatic cancer

- Little role for local therapies
 - Radiation for symptomatic metastases

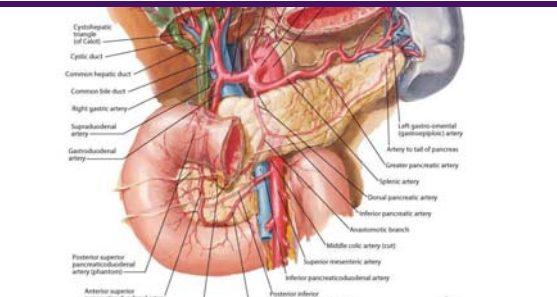


Natural history of pancreatic cancer


- Surgical resection is the only path to cure
- “Practical” staging system
 - Potentially resectable –20%
 - Locally advanced/borderline resectable → 30%
 - Locally advanced/unresectable
 - Metastatic—50%



Natural history of pancreatic cancer



http://www.netterimages.com




Natural history of pancreatic cancer

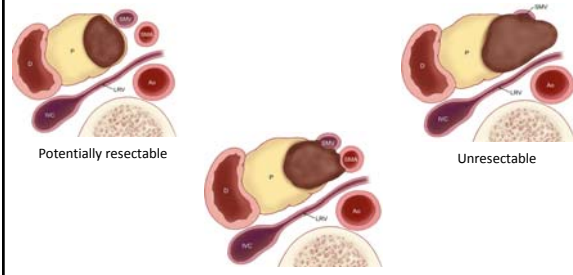
NCCN Guidelines Version 2.015
Pancreatic Adenocarcinoma

CRITERIA DEFINING RESECTABILITY STATUS ¹	
Resectability Status	Arterial
Resectable	No arterial tumor contact (cut or CA) superior mesenteric artery (SMA), or common hepatic artery (CHA).
Borderline Resectable²	Epistemic based (epistemic process): <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA or IVP. • Presence of variant arterial anatomy (ie, accessory right hepatic artery, celiac or right hepatic artery, replaced CA) and the origin of hepatic or accessory artery and the presence and degree of tumor contact should be noted if present as it may affect surgical planning. Epistemic based (cut): <ul style="list-style-type: none"> • Solid tumor contact with the CA of IVP. • Solid tumor contact with the CA of IVP without involvement of the artery and with intact and antitumoral pancreaticoduodenal artery (some members prefer this criteria to be in the unresectable category).
Unresectable³	Unresectable process: <ul style="list-style-type: none"> • Unresectable IVP/IVC due to tumor involvement or extension that is due to tumor or blood thrombus. • Contact with most proximal draining jejunal branch into IVP. Body and tail: <ul style="list-style-type: none"> • Unresectable IVP/IVC due to tumor involvement or extension (can be due to tumor or blood thrombus).


¹ NCCN guidelines. Pancreatic adenocarcinoma. (Version 2.015). http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf Accessed 2 December 2015.



Natural history of pancreatic cancer




http://www.froedtert.com/liver-pancreas-bile-duct-cancer/pancreatic-cancer/education



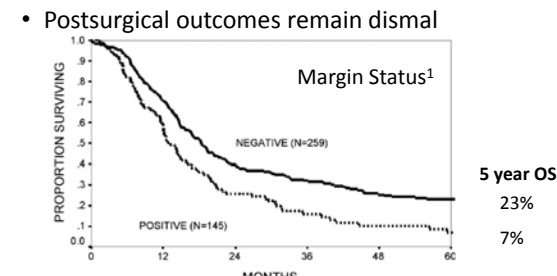
Natural history of pancreatic cancer

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Resectable pancreatic cancer

- Postsurgical outcomes remain dismal



¹ Cameron, et al. Ann Surg. 2006;244:10–15.
² Oettle H, JAMA. 2007;297(3):267.



Resectable pancreatic cancer

- Postsurgical outcomes remain dismal

Node Status¹

5 year OS
32%
14%

¹ Cameron, et al. Ann Surg. 2006;244:10-15.
² Oettle H, JAMA. 2007;297(3):267.

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Resectable pancreatic cancer

- Postsurgical outcomes remain dismal
- 5 year overall survival: 15-25%^{1,2}

5 year OS (all patients) 18%
5 year OS (R0 and N0) 41%

¹ Cameron, et al. Ann Surg. 2006;244:10-15.
² Oettle H, JAMA. 2007;297(3):267.

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Resectable pancreatic cancer

- Postsurgical outcomes remain dismal
 - 5 year overall survival: 15-25%^{1,2}
- Potential ways to improve outcome
 - New surgical strategies
 - Adjuvant therapy (chemotherapy, radiation)
 - Neoadjuvant therapy

¹ Cameron, et al. Ann Surg. 2006;244:10-15.
² Oettle H, JAMA. 2007;297(3):267.

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Adjuvant chemotherapy

- Chemotherapy alone¹
 - Gemcitabine (CONKO-01 trial)
 - Gemcitabine (3 weeks/4) x 6 months vs. observation
 - Gemcitabine....
 - Delayed progression compared to observation (13.4 mo v. 6.7 mo)
 - Improved 5 year OS compared to observation (20.7 v. 10.4 %)
- Chemoradiation
 - Considerable controversy regarding benefit
 - Typically utilized in US to decrease local recurrence

¹ Oettle H, JAMA. 2007;297(3):267.

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Why neoadjuvant chemotherapy?

- Theoretical benefits of neoadjuvant therapy
 - Downsize "borderline resectable" tumors to resectable
 - Increase rate of margin negative resections
 - Importance of R0 resection as prognostic factor
 - Eliminate micrometastatic disease earlier in course
 - Importance of N0 disease as prognostic factor
 - Allows patients to go into chemotherapy without surgical morbidities
 - Identify patients for whom aggressive therapy will provide no benefit

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Neoadjuvant therapy

- Approach experimental, outcomes unclear...
 - No standard definition of resectability
 - No standard approach to neoadjuvant treatment
 - No standard approach to response criteria

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Natural history of pancreatic cancer

<http://www.froedtert.com/liver-pancreas-bile-duct-cancer/pancreatic-cancer/education>

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Neoadjuvant therapy

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 - No standard definition of resectability
 - No standard approach to neoadjuvant treatment
 - No standard approach to response criteria
- Data is on case series level

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Neoadjuvant therapy

- MD Anderson experience¹
 - 160 patients with “borderline resectable” disease
 - Group A: Borderline vascular involvement N=84
 - Group B: Indeterminate metastatic disease N=44
 - Group C: Poor performance status N=32
 - Neoadjuvant therapy
 - 75% received chemotherapy
 - Gemcitabine alone or in combination
 - 95% received chemoradiation
 - RT given with “concurrent 5-fluorouracil, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses”

¹ Katz, et al. J Am Coll Surg. 2008. May;206(5):833-46

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Neoadjuvant therapy

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Neoadjuvant therapy

- MD Anderson experience¹
 - Surgical outcomes
 - 62/66 (94%) had R0 resection
 - 40/66 (61%) had N0 resection
 - Survival outcomes

	Median survival	5 year OS
All patients	18 months	18%


¹ Katz, et al. J Am Coll Surg. 2008. May;206(5):833-46

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Neoadjuvant therapy

- Meta-analysis of phase II trials¹
 - Significant heterogeneity in approaches
- 5 studies with 134 borderline resectable cases
 - 42 patients (32%) were able to proceed with resection
 - 26 patients (62% of resected) had R0 resection
- Median survival:
 - All patients: 11.2 months
 - Resected patients: 22.3 months


¹ Assifi, et al. Surgery. 2011 September ; 150(3): 466-473.



Neoadjuvant therapy

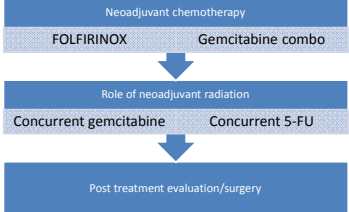

- Neoadjuvant therapy in the FOLFIRINOX era
 - Blazer, et al¹
 - 39 patients received FOLFIRINOX
 - 19 borderline resectable and 20 LA-unresectable
 - Most underwent chemotherapy and chemoradiation
 - Borderline resectable only subgroup
 - 12/19 (63%) underwent resection; 10/12 R0 resections

¹ Blazer, et al. J Clin Oncol 32, 2014 (suppl 3; abstr 275)

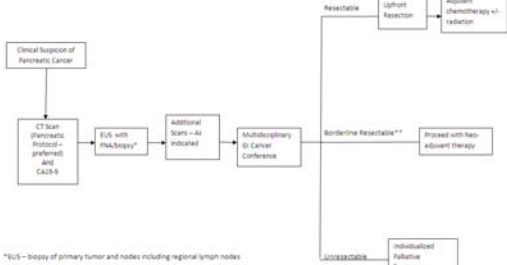


Ongoing research...

- At least 27 open trials on clinicaltrials.gov
 - Majority evaluating safety of various approaches


Sanford approach



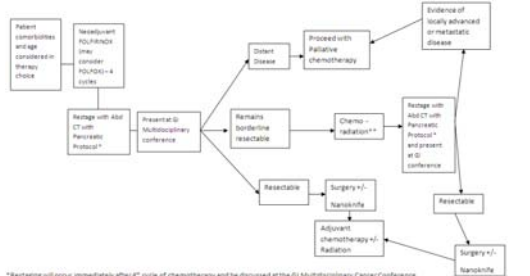
^{*}EUS - biopsy of primary tumor and nodes including regional lymph nodes

^{**}Borderline resectable criteria per Sanford Protocol

1. SMA, hepatic, or Celiac involvement (>180 degrees)
2. No encasement of SMV/Portal confluence. (venous involvement reviewed at multidisciplinary conference)
3. Involvement of lymph nodes including regional lymph nodes
4. Co-morbidities reviewed for surgical risk at multidisciplinary conference




Sanford approach




^{*}Re-staging will occur immediately after 4th cycle of chemotherapy and be discussed at the GI Multidisciplinary Cancer Conference

^{**}Cisplatin/5FU and Radiation (5FU given over 20 - 28 treatments) - RTOG 0848 weeks post-resection completion and discussion at the GI Multidisciplinary Cancer Conference



Summary

- Outcomes in pancreatic cancer are poor even with advancements in chemotherapy, surgical technique
- Quality of surgical resection is a major predictor of long term outcomes
- Neoadjuvant approaches MAY improve surgical resectability and hence, outcomes



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Patient's perspective

- June 2014
 - Presents with abdominal pain and weight loss
 - Imaging reveals pancreatic tail mass
- July 2014
 - Undergoes distal pancreatectomy/splenectomy
 - Pathology:
 - 4.0 cm pancreatic adenocarcinoma
 - Negative margins
 - 5/12 lymph nodes positive



Patient's perspective

- September-December 2014
 - Weekly gemcitabine x 3 cycles
- January-February 2015
 - Concurrent chemoradiation with 5-fluorouracil
- April-June 2015
 - Weekly gemcitabine x 3 cycles



Patient's perspective

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Patient's perspective



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