Pancreatic cancer: what’s the latest

Katy Morgan, MD, FACS
Professor and Chief, Division of GI and Laparoscopic Surgery
Medical University of South Carolina
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The problem

• Pancreatic cancer is the third most common cause of cancer related death in the US
• In 2019, an estimated 56,770 new cases of pancreatic cancer will be diagnosed and 45,416 pancreatic cancer related deaths will occur
• The median survival of even most favorable pancreatic cancers remains between 2-2.5 years
• Less than 50% of patients with localized pancreatic cancer receive both surgery and chemotherapy
• *critical reassessment of the status quo needed*
  • Pancan.org, cancer.org, Dimou JOGS 2016
Pancreatic Cancer: Stage at Presentation

- Resectable disease: localized disease with no major vessel involvement
- Borderline resectable (BRPC): <180 abutment of vessels
- Locally advanced (LAPC): involvement of SMA, celiac axis
- Metastatic: distant mets, peritoneal implants, portal or retroperitoneal LAD

Definitions:

- Resectable: 15%
- BRPC/LAPC: 45%
- Metastatic: 40%

Ries SEER Cancer Statistics Review.
• **Resectable**
  – no evidence of extra-pancreatic disease
  – <180 degree involvement of SMV/PV
  – Normal tissue plane between tumor and the celiac, CHA, or the SMA.

• **Borderline resectable**
  – >180 degree involvement of SMV/PV, reconstructable
  – evidence of tumor abutment (< 180 degree or 50% vessel circumference) against celiac, CHA, or SMA

• **Locally advanced**
  – SMV/PV involvement with no option for reconstruction
  – arterial encasement (> 180 degree or 50% vessel circumference) of celiac, CHA, or SMA
Current standard of care for localized (nonmetastatic) disease

• Surgery and perioperative chemotherapy
• (perioperative radiotherapy)
• Traditionally surgery precedes chemotherapy
• Sequence increasingly controversial
• Evidence insufficient
• NCCN guidelines
NCCN guidelines

<table>
<thead>
<tr>
<th>NCCN Classification</th>
<th>Venous</th>
<th>Arterial</th>
<th>Treatment recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>&lt;180 contact w SMV/PV</td>
<td>No contact</td>
<td>Primary resection</td>
</tr>
<tr>
<td>Borderline resectable</td>
<td>&gt;180 contact w SMV/PV, suitable for reconstruction</td>
<td>&lt;180 contact w SMA or celiac axis</td>
<td>Preoperative chemotherapy</td>
</tr>
<tr>
<td>Locally advanced Unresectable</td>
<td>Unreconstructable SMV/PV due to tumor involvement</td>
<td>&gt;180 contact w SMA or celiac axis</td>
<td>Chemotherapy, possible reassessment for resectability</td>
</tr>
</tbody>
</table>
Current trend:

• Neoadjuvant therapy considered in all cases of localized pancreatic cancer (including Resectable)

• Broader definition of Borderline Resectable (dictating neoadjuvant rx)
  • Type A: Anatomy (vascular abutment of any kind)
  • Type B: Biology (elevated CA19-9)
  • Type C: Comorbidity (poor patient physiology)

• Supported by ASCO clinical practice guidelines
Rationale (and a little evidence) for the neoadjuvant approach

**Multimodal therapy is essential**

- **CONKO-001 trial**
  - Randomized pts after resection to gemcitabine vs observation
  - Median DFS 13.4 vs 6.7 mos ($p<0.001$), OS 22.8 vs 20.2 mos ($p<0.01$)
    - Oettle JAMA 2007
- **Canadian Cancer Clinical Trials Group and Unicancer-GI—PRODIGE group**
  - Adjuvant FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, fluorouracil) vs gemcitabine
  - Median DFS 21.6 vs 12.8 mos ($p<0.001$), OS 54.4 vs 35 mos ($p=0.003$)
  - FOLFIRINOX higher toxicity (76% vs 53%)
    - Conroy NEJM 2018
Neoadjuvant approach

**Neoadjuvant chemotherapy ensures chemotherapy is given**

- Recent review of NCD data shows only 58% of pts with primary resection receive adjuvant therapy
  - Dimou JOGS 2016

- Pts who have major complications after primary surgery have survival rates similar to those whose surgery was abandoned due to metastatic disease
  - Tzeng JOGS 2014

- Pts who receive preoperative chemotherapy and have major surgical complications have OS similar to patients without complications
  - Tzeng JOGS 2014
Neoadjuvant approach

Pancreatic cancer is a systemic disease

• 90% of recurrences within 6 months of surgery are distant
  • Groot Ann Surg 2017

• Pts w greater than 20 day interval from diagnosis to resection have an increased risk of metastatic disease discovered at surgery
  • Glant Surgery 2011

• Neoadjuvant therapy allows for earliest systemic therapy without delay due to surgery (uncomplicated or complicated)
Neoadjuvant approach

Neoadjuvant therapy does not make surgery more morbid

• Verona, 445 pts undergoing pancreatic resection for pdac
• Those w neoadjuvant rx had lower rates of POPF and perioperative hemorrhage, but increased DGE
  • Marchegiani Ann Surg Oncol 2018
Neoadjuvant approach

**Neoadjuvant therapy can decrease margin positivity**
• Rates of margin positivity are high, 33-85%
  • Butler HPB 2016, Verbeke Br J Surg 2012
• Locoregional recurrence is common, 80% in one autopsy study
  • Iacobuzio-Donahue J Clin Oncol 2009
• Pts undergoing neoadjuvant chemotherapy and XRT have been shown to have lower rates of positive margins than those undergoing primary resection
  • Katz JOGS 2012, Karofa Radiother Oncol 2014
• Neoadjuvant chemo and XRT yields lower local recurrence risk than neoadjuvant chemo alone
  • Cloyd Cancer 2016
• Neoadjuvant delivery of chemo/XRT is theoretically advantageous given intact vasculature and oxygenated target tissue
Neoadjuvant approach

Neoadjuvant therapy allows for best patient selection

- Declaration of distant metastases
- Declaration of patient’s functional status
- Evaluate *in vivo* chemoresponsiveness
Neoadjuvant approach: some outcomes

• Two multicenter randomized studies in US and in Europe failed to enroll
  • Casadei JOGS 2015

• MGH experience in 188 pts, 40 received Folfirinox, tumor response not appreciated on 28/40 CT. Less operative morbidity (POPF), 92% R0 resection, decreased LN positivity, perineural invasion, increased OS
  • Ferrone Ann Surg 2015

• Heidelberg experience 575 pts w locally advanced pdac, 61% resection rate after FOLFIRINOX
  • Hackert Ann Surg 2016
Neoadjuvant approach: some outcomes

- 2 NCD reviews show more negative margins, less nodal disease, and improved survival in locally advanced pdac w neoadjuvant therapy
  - Shubert Surgery 2016, Youngwirth J Surg Oncol 2017
- Meta-analysis of patients with locally advanced pdac rx’d with FOLFIRINOX demonstrated a 28% resection rate, 74% R0
  - Suker Lancet Oncol 2016
- Alliance trial shows efficacy of preop FOLFIRINOX with CRT in borderline resectable patients, with 68% undergoing surgery, 93% R0 rate, and 21 mo median survival
  - Katz JAMA Surg 2016
Radiation therapy: unclear role

• Adjuvant CRT:
  • GITSG 1985 survival benefit; 2 large trials since show no benefit. Large retrospective study from Hopkins showed benefit
    • Kalser Arch Surg 1985, Herman J Clin Oncol 2008

• Neoadjuvant CRT:
  • Large Phase II trial of neoajuvant gem +50 Gy—resection rate 87%, R0 99%, 5 yr survival 57%
    • Takahashi Ann Surg 2013

• Newer Techniques:
  • Stereotactic Body Radiation Therapy (SBRT)
    • Rashid Ann Surg Oncol 2016
  • Intraoperative Radiation Therapy (IORT), Mobetron
Locally directed therapies

• Pancreatic cancer is heterogeneous
• Rapid autopsy study by Embuscado looked at mutational genetics of pancreatic ca
• Found that locally advanced pancreatic cancer and metastatic pancreatic cancer are genetically different
• there are locally advanced tumors that do not disseminate systemically
• This conclusion opens the window for locally directed therapies
  • Cancer Biol Ther 2005
Can we differentiate clinically local predominant tumors from those likely to metastasize

• SMAD4 (dpc4) is a histologic marker. Intact SMAD4 is associated with local progression, loss of SMAD4 is correlated w metastatic ca
  • Iacobuzio-Donahue J Clin Oncol 2009, Crane J Clin Oncol 2011

• SMAD4 status not reliably determined via EUS biopsy

• CA19-9 response post chemotherapy can predict improved survival and help with patient selection for surgery
  • Berger J Clin Oncol 2008, Hurt Br J Cancer 2017
Locally directed therapies
Bigger surgery—vascular resection

• Portal vein resection

• Introduced in the 1970s by Fortner
  • Surgery 1973

• Early experience did not demonstrate survival advantage
  • Yeo Ann Surg 2002, Riall JOGS 2005
Venous resection

• Multiple single center studies and 2 meta-analyses have shown no difference in morbidity, mortality for PD with PV reconstruction vs standard PD

• A NSQIP review and the largest available meta-analysis did show increased morbidity

• Patency rates high, 7-13% occlusion at 1 yr fu, no benefit of anticoagulation demonstrated
Venous resection

• Multiple single center studies and a meta-analysis have shown similar overall survival rates bt pts undergoing PD w or wo venous reconstruction

• Positive margins and tumor invasion of the resected vein are predictive of poorer survival

• Important to emphasize the role of neoadjuvant therapy in these outcomes
Arterial resection

• Introduced by Appleby in the 1950s w resection of the celiac axis, with DP and total gastrectomy for gastric ca; subsequently applied in the 1970s to pancreatic ca
  • Appleby Cancer 1953

• More controversial than venous resection and not universally accepted

• Due to anatomic proximity, arterial resections for tumors of the pancreatic head often require concomitant PV resection

• Several small studies have demonstrated reasonable outcomes for arterial resection w pancreatic head tumors
  • Tseng JOGS 2004, Chua JOGS 2010
Arterial resection

• Locally advanced pancreatic body tumors with celiac axis involvement can be treated with *en bloc* arterial resection, aka modified Appleby procedure, DP-CAR

• Requires intact flow through GDA to proper hepatic artery or bypass

Smoot JOGS 2012
Arterial resection

• Numerous reports indicate comparable overall survival bt DP-CAR and standard DP, with median survival 10 to 26 mos. Morbidity rates range broadly from 29-92%

• A recent meta-analysis demonstrated no difference in mortality, morbidity, or survival, w an avg R0 resection rate of 73% for DP-CAR
  • Gong Medicine 2016
Ablative therapies

• Radiofrequency Ablation (RFA)
• Cryosurgery
• High Intensity Focused Ultrasound (HIFU)
• Irreversible Electroporation (IRE)
Irreversible electroporation (IRE, Nanoknife)

• Nonthermal ablative technology, uses short pulses of high voltage direct current to (irreversibly) alter cell permeability and induce cell death
• Does not disrupt extracellular matrix and therefore no injury to adjacent vasculature, no heat sink
• Indicated for locally advanced pancreatic cancer after neoadjuvant chemotherapy and nonprogression of disease (Stage III)
• In-situ tumor treatment or in combination with resection for margin enhancement
Irreversible electroporation (IRE, Nanoknife)
Irreversible electroporation (IRE, Nanoknife)

- 54 pts undergoing IRE for stage III pdac matched to 85 pts stage II undergoing chemotherapy and radiation alone
- Disease free survival (14 vs 6 mos) and overall survival (21.2 vs 11 mos) better in IRE
  
  Martin Ann Surg Oncol 2013

- 200 pts undergoing IRE for stage III pdac
- All pts underwent neoadjuvant chemorx, 52% also had XRT, before IRE
- 150 had IRE alone to in situ tumor, 50 had resection plus IRE margin enhancement
- median OS 24.9 mos (range 4.9-85 mos)
  
  Martin Ann Surg 2015
Irreversible electroporation (IRE, Nanoknife)

IMPALA Study
- Induction chemorx (folfox or gemcitabine), ex lap, resection or IRE
- Median survival after resection, IRE, and for all patients with nonprogressive disease without resection 34, 16, and 15 mos respectively
  - Vogel Ann Surg Oncol 2017
Extended indications for surgery

- Oligometastatic disease? Tumors with favorable biology?

- Italians reported on 127 pts with hepatic metastases from pdac who underwent rx with chemotherapy
  - 56 pts (44%) had a complete (7%) or partial (37%) response
  - 11 underwent resection
  - Median OS for entire cohort 11 mos vs 15 mos for those with response
  - Median survival longer for pts undergoing resection 46 vs 11 mos(p<0.001)
  - Not standard, should only be undertaken in setting of a clinical trial
    - Crippa EJSO 2016
Multidisciplinary tumor board

- Medical Oncology
- Radiation Oncology
- Surgery
- Gastroenterology
- Interventional Radiology
- Diagnostic Radiology
- Pathology
- Research Coordinators
Conclusions

• Multimodality therapy is essential for best outcomes in pancreatic ca
• Multidisciplinary team is key
• Neoadjuvant therapy is the optimal approach in most patients with localized pancreatic cancer
• Pancreatic cancers have a heterogeneous biology and some have a locally predominant pattern. These cancers may be amenable to locally directed therapies
• The future of pancreatic cancer is in elucidating genetics of specific cancers to allow for targeted therapies