Multidisciplinary Palliative Management in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Potential Management</th>
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<tbody>
<tr>
<td>Pain</td>
<td>Analgesics (intrac)</td>
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<td></td>
<td>Radiation therapy</td>
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<td></td>
<td>Celiac plexus neurolysis</td>
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<tr>
<td>Gastric Outlet Syndrome</td>
<td>Prophylactic gastrojejunostomy in unresectable patients during exploratory surgery</td>
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<td>Jaundice</td>
<td>Endoscopic stent placement</td>
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<td>Biliary decompression can be achieved through</td>
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<td>Choledochojjunostomy</td>
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<td>Cholecystojjunostomy</td>
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Advances in the Treatment of Pancreatic Cancer

• Better endoscopy (diagnostic and therapeutic)
• Improved pre-operative imaging
• Surgical resections safer
• Pre-operative therapy has allowed resections in patients that would have previously been deemed unresectable
• Median survival has improved with more active systemic chemotherapy
• Earlier and better palliative and supportive care
  • But we still have not made major breakthroughs that have a significant survival impact in most patients

Pancreatic Cancer Positive Trials.

<table>
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<tr>
<th>Year Range</th>
<th>5 year Survival</th>
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<tr>
<td>1991-2000</td>
<td>4.4%</td>
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<tr>
<td>2001-2010</td>
<td>6.3%</td>
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<td>2006-2012</td>
<td>7.7%</td>
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<td>2010-2021</td>
<td>9.2%</td>
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Adapted from Monica Tang MD PhD.
SEER analysis 2010-2021
5 year Survival 10%

Improving Survival

Kardosh et al., Pancreas. 2018
Pathophysiology

~90% is ductal adenocarcinoma, which is characterized by:

1. Poor vascularization, which creates a barrier for effective cytotoxic delivery
2. An enveloping fibrotic stroma of excessive connective tissue and cells that forms hard tumors

Disease Site

- Pancreatic
  - Resectable
  - Locally Advance
  - Metastatic

Resectable Pancreatic Adenocarcinoma

- NeoOptimize Switch - Phase II
  - Adaptive switching of mFOLFIRINOX or Gemcitabine/nab-Paclitaxel as a neoadjuvant strategy
  - WOO-S (SMMART)
    - Serial biopsies to assess the biological impact of targetable therapies and evaluation of potential future combination therapy
Resectable Pancreatic Adenocarcinoma
Locally advance Pancreatic Adenocarcinoma

Manipulation of cancer metabolism

- Dependence of tumor cells on exogenous asparagine.
- L-asparaginase can be exploited to deplete extracellular asparagine.
- But, oncogenic KRAS mediates metabolic reprogramming shifts dependence from asparagine via RAS signaling.
- Preclinical mouse models MEK inhibitor plus L-asparaginase treatment reduced tumor growth!!!
Metastatic Pancreatic Adenocarcinoma

1st Line
Morpheus - Phase II
Multiple Immunotherapy-Based Treatment Combinations with Gemcitabine + Nab-Paclitaxel

2nd Line
NAPOLI Phase III
Liposomal Irinotecan/5FU/Leu/Oxali

3rd Line +
WOO - M (SMMART)
Serial biopsies to assess the biological impact of targetable therapies and evaluation of potential future combination therapy.