Neoadjuvant Chemotherapy for Resectable Pancreatic Cancer: Where We Stand

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WHY?

Data from the NIH/SEER program

<table>
<thead>
<tr>
<th>Estimated New Cases in 2019</th>
<th>56,770</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated Deaths in 2019</th>
<th>45,750</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All Cancer Deaths</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Percent Surviving 5 Years

9.3%

2009-2015

Allegheny Health Network
WHY?

Data from the NIH/SEER program

**Pie Chart 1:**
- **52%** Localized (10%) Confined to Primary Site
- **29%** Regional (29%) Spread to Regional Lymph Nodes
- **8%** Distant (52%) Cancer Has Metastasized
- **8%** Unknown (8%) Unstaged

**Bar Chart 2:**
- **34.3%** Localized
- **11.5%** Regional
- **2.7%** Distant
- **5.5%** Unknown

Stage
Rationale for Neoadjuvant chemotherapy

• 40-50% of patients having undergone curative resection do not receive the adjuvant treatment planned due to surgical complications, poor performance status, comorbidity, patient refusal, and/or early disease recurrence

• Chemotherapy administered before surgery to non-dissected, well-oxygenated tissue may maximize any potential benefit compared to post op tissue
Rationale for Neoadjuvant chemotherapy

• May decrease tumor volume, thus improving R0 resectability and completion of multimodal treatment
• Minimize regional nodal disease/micrometastasis, hence reducing the risk of loco-regional recurrence.
• Identify aggressive tumors; avoiding futile surgery
Data from AHN


(n=70) Resectable patients

(n=64) Underwent R0/R1 resection

(n=37) 58% Started Adjuvant chemotherapy

(n=16) 25% Completed Adjuvant chemotherapy

Kaplan-Meier curves for overall survival based on adjuvant chemotherapy (P = 0.43) and (B) number of adjuvant chemotherapy cycles received (P = 0.014).
Argument against neoadjuvant

- Since surgery is the only potential cure, toxic neoadjuvant regimen may be harmful as these could hamper the surgical outcome
- Risk of disease progression under therapy
- Lack of randomized controlled data- most of the literature on neoadjuvant treatment is from patients with borderline or locally advanced (unresectable) pancreatic cancer without concrete evidence
Data thus far

• 1992: Single arm single center data from MD Anderson in a study by Evans et al.
• Multitude of studies but most combine resectable and borderline resectable (some with locally advanced) for neoadjuvant chemotherapy and radiation therapy.
• Low strength data- Systematic review and metanalysis by Bradley et al. in 2019: 452 studies reviewed; 9 offered comparison between NAT and surgery followed by adj for treatment of RPC; only 1 RCT (which was terminated early)
• Mixed results without conclusive evidence to change current guideline
Data thus far

• Difficult to interpret:
  – No standardization of definition of resectable disease
  – No standardization of neoadjuvant chemotherapy regimen
  – Neo adjuvant chemo vs chemoradiation
  – Selection bias: patients who did not undergo surgery after Neoadj therapy were not included in survival analysis
  – Selection bias based on surgical team preference: location of tumor and ease of surgery
  – Difficulty in recruitment due to patient preference for surgery
Major studies underway

- Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (includes BRPA)- Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic cancer (JSAP)
Major studies underway

- Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - a national multicenter randomized controlled trial.
  - Panc head cancers only
  - Primary end point is overall mortality in patient who undergo resection
  - Secondary endpoint is overall survival after randomization with ITT analysis
Major studies underway

- Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study)
  - French study
  - evaluating the safety and efficacy of two regimens of neo-adjuvant chemotherapy (4 cycles of mFOLFIRINOX or FOLFOX) relative to upfront surgery and adjuvant chemotherapy in patients with resectable PDAC
Neoadjuvant chemo for resectable PDA at AHN

- MDPC started neoadjuvant protocol for resectable head and neck PDA per NCCN criteria
- Tail cancers not included---Onc Surgery consensus---easy resectablility with distal pancreatectomy which has low morbidity.
- Ongoing prospective data collection since Oct 2018
Performance status good/Age < 65 - Modified FOLFIRINOX
Performance status poor/Age > 65 - Gemcitabine + Abraxane

Neo-ajd chemo regimen - [once/week for 3 weeks + 1 week drug holiday] X 4 cycles

Restaging at 2 and 4 months: CT abd pelvis panc protocol + CA 19-9

Surgery if still resectable

Adjuvant chemotherapy
End points

• Primary
  – Survival at 1, 2 and 5 years

• Secondary
  – Tolerability of neoadjuvant chemotherapy
  – Patients undergoing surgery
  – R0 resection margins
**Preliminary results**

<table>
<thead>
<tr>
<th>Count</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>• Resectable head and neck PDA</td>
</tr>
<tr>
<td>8</td>
<td>• Started neo-adj chemo</td>
</tr>
<tr>
<td>4</td>
<td>• Currently undergoing neo-adj chemo</td>
</tr>
<tr>
<td>2</td>
<td>• Completed and underwent resection</td>
</tr>
<tr>
<td>2</td>
<td>• Lost to follow up</td>
</tr>
<tr>
<td>7</td>
<td>Non surgical candidates due to poor functional status</td>
</tr>
<tr>
<td>2</td>
<td>Patient preference</td>
</tr>
<tr>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>1</td>
<td>Unknown reason</td>
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</table>
Where do we stand?

- Standard of care for resectable pancreatic cancer remains surgery + adjuvant chemotherapy
- Increasing evidence regarding improved outcomes with Neoadjuvant treatment are emerging (however, with debatable and conflicting results) underlining the need for robust randomized controlled trials in the field
- Until then, regional and institutional protocols based on multidivisional consensus and patient preference dictate the care pathway followed
References


• Fuyuhiko et al. Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic cancer (JSAP), Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05), Japanese Journal of Clinical Oncology, Volume 49, Issue 2, February 2019, Pages 190–194

• Schwartz et al. Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study) BMC Cancer. 2018; 18: 762.


Thank you