Neoadjuvant Chemotherapy for Resectable Pancreatic Cancer: Where We Stand

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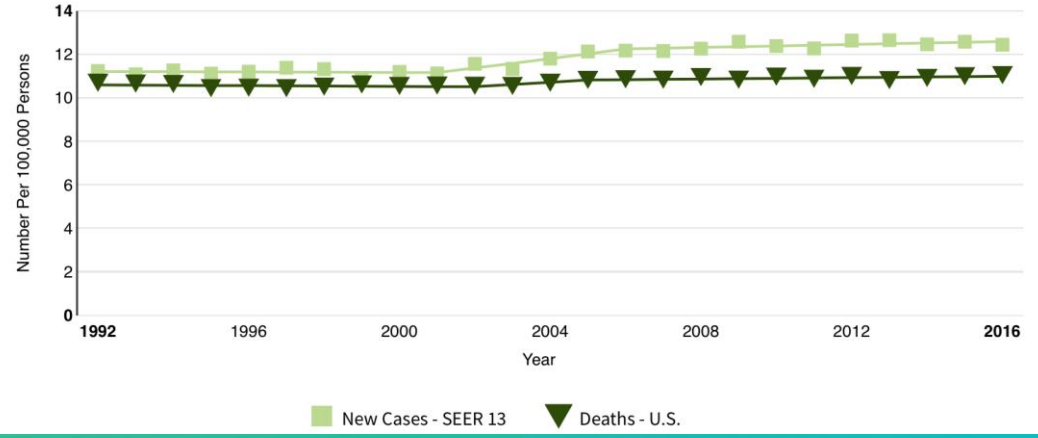
WHY?

Estimated New Cases in 2019	56,770
% of All New Cancer Cases	3.2%

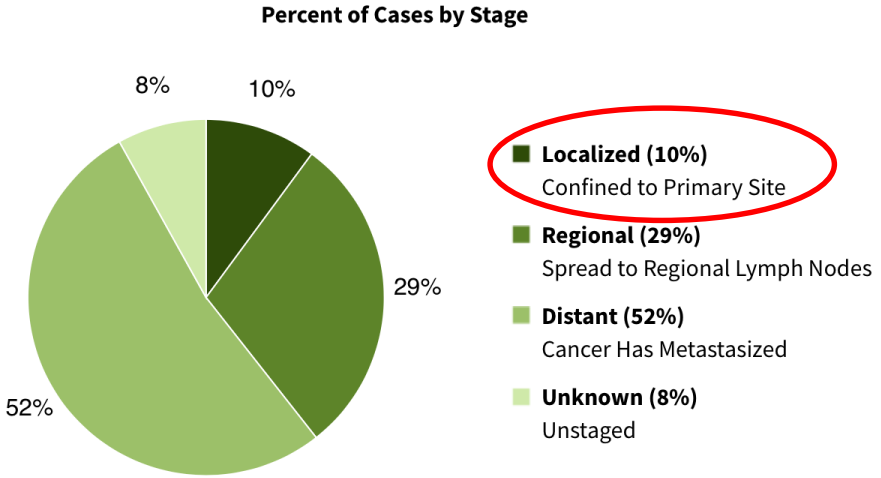
Estimated Deaths in 2019	45,750
% of All Cancer Deaths	7.5%

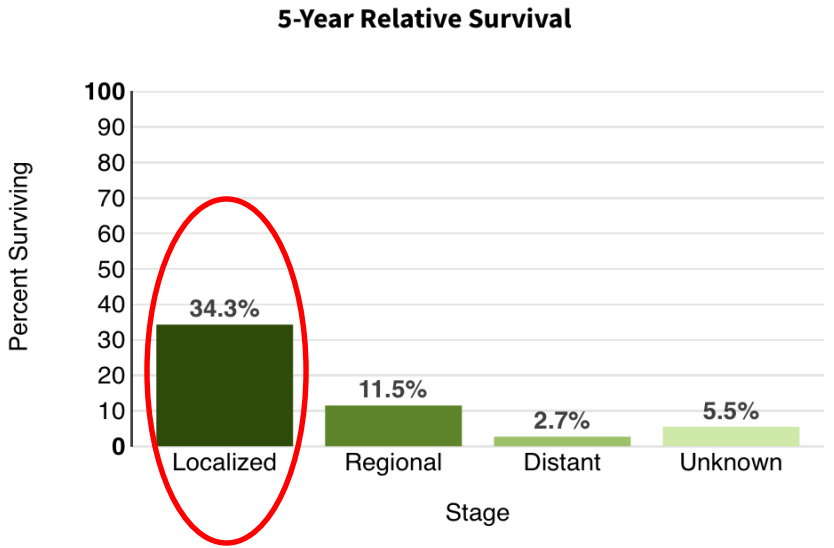
Percent Surviving 5 Years
9.3%
2009-2015



Data from the NIH/SEER program

WHY?





Data from the NIH/SEER program

Rationale for Neoadjuvant chemotherapy

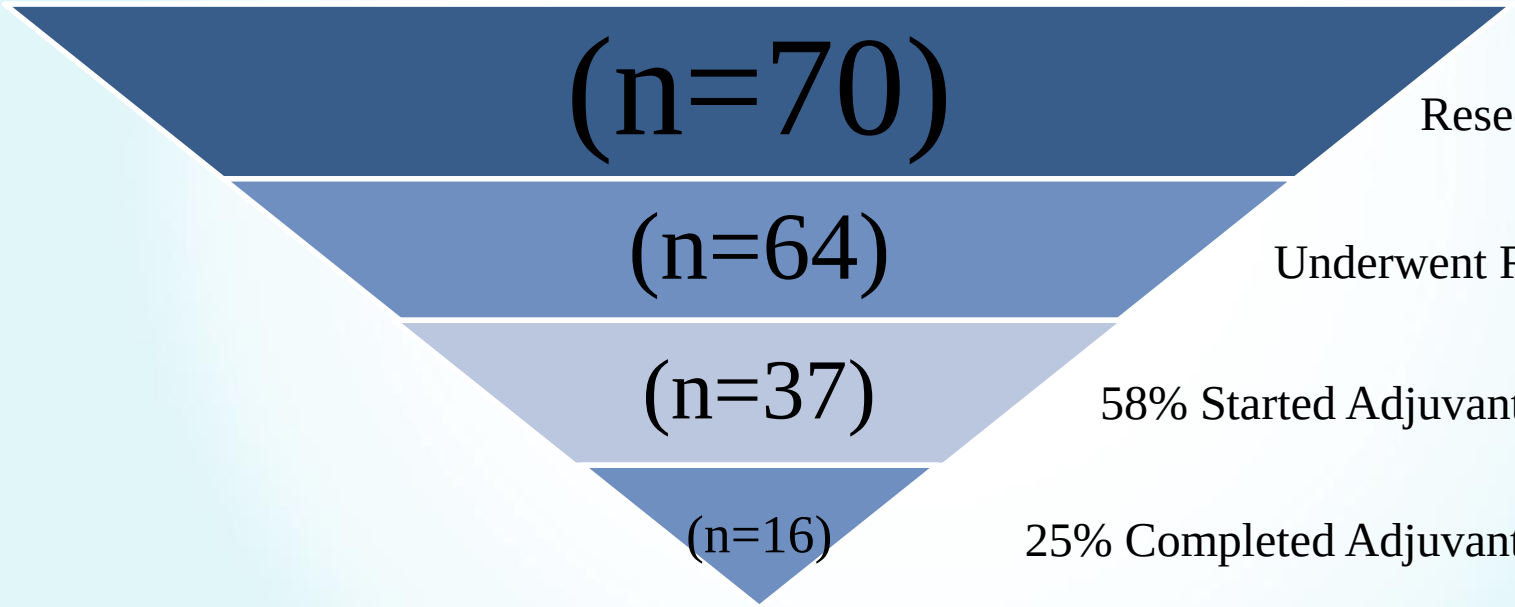
- 40- 50% of patients having undergone curative resection do not receive the adjuvant treatment planned due to surgical complications, poor performance status, comorbidity, patient refusal, and/or early disease recurrence
- Chemotherapy administered before surgery to non-dissected, well-oxygenated tissue may maximize any potential benefit compared to post op tissue

Rationale for Neoadjuvant chemotherapy

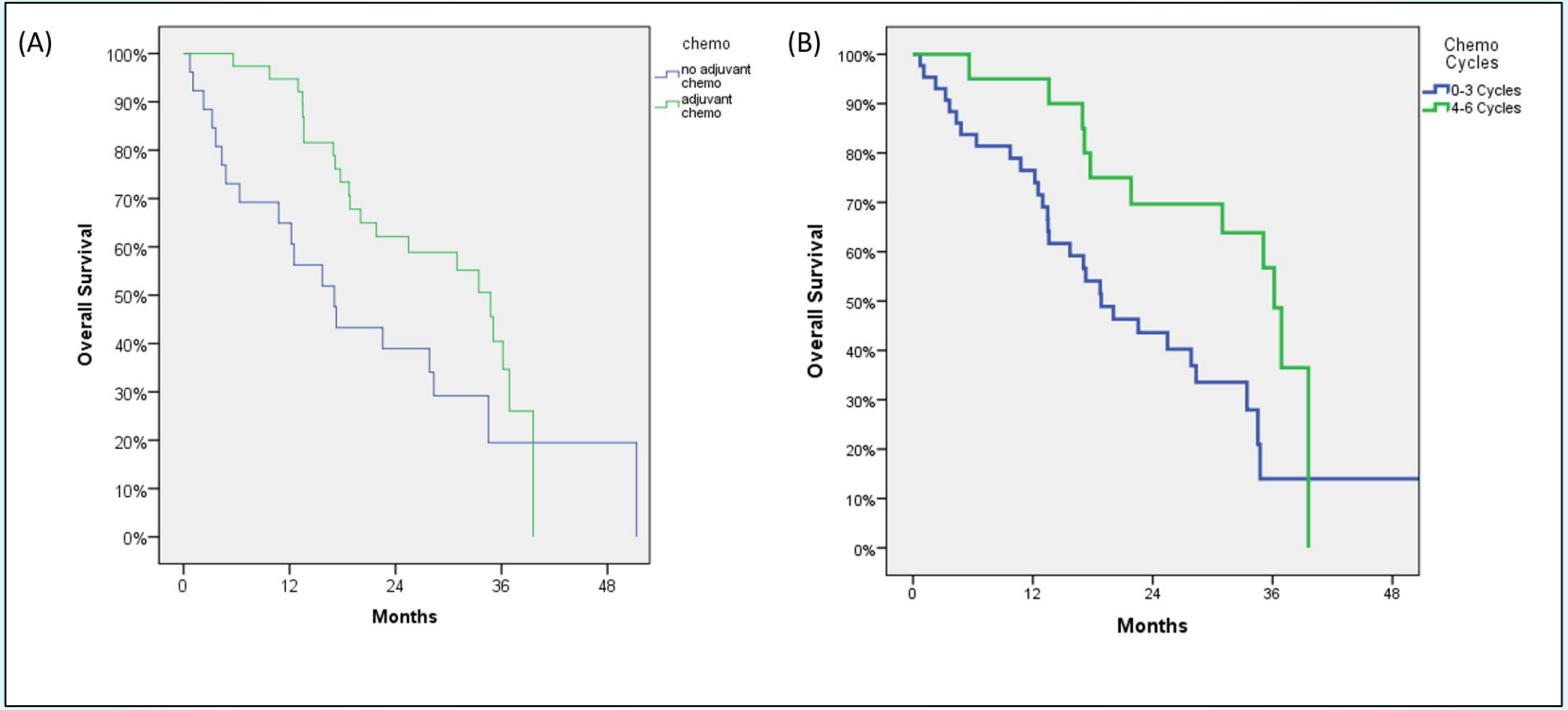
- May decrease tumor volume, thus improving R0 resectability and completion of multimodal treatment
- Minimize regional nodal disease/micrometastasis, hence reducing the risk of loco-regional recurrence.
- Identify aggressive tumors; avoiding futile surgery

Data from AHN

- **Survival Trends for Resectable Pancreatic Cancer Using a Multidisciplinary Conference: The Argument for Neoadjuvant Chemotherapy**



Rao B. et al. Performance of MDPC in predicting and managing Resectable Pancreatic Cancer.. Pancreas Jan 2019; 48(1):80-84 PMID: 30451791



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

Syed et al. Survival Trends for Resectable Pancreatic Cancer Using a Multidisciplinary Conference: The Argument for Neoadjuvant Chemotherapy. Ahead of print Journal of Gastrointestinal Cancer

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

19	• Resectable head and neck PDA
8	• Started neo-adj chemo
4	• Currently undergoing neo-adj chemo
2	• Completed and underwent resection
2	• Lost to follow up

7	Non surgical candidates due to poor functional status
2	Patient preference
1	Died
1	Unknown reason

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

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Thank you