Neoadjuvant Chemotherapy for Resectable Pancreatic Cancer: Where We Stand

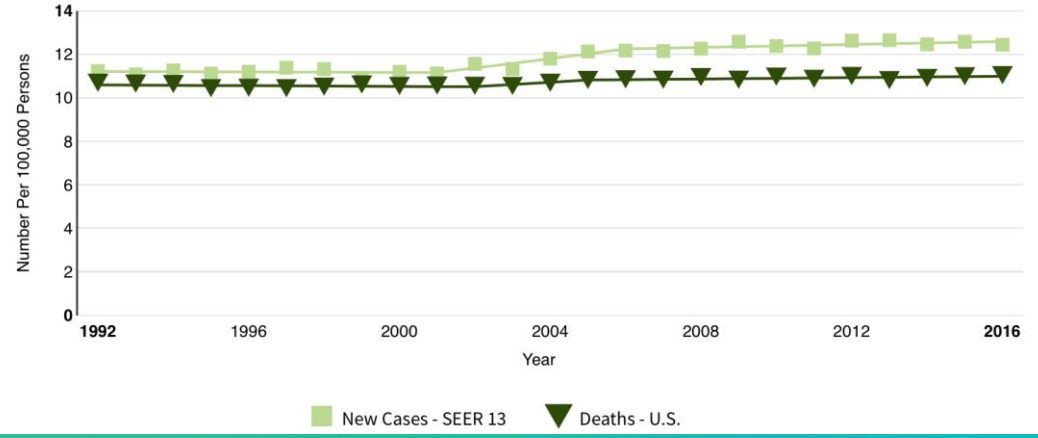
Manav S. Sharma, MD
Walter G. Park, MD, MS
Shyam J. Thakkar, MD

WHY?

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

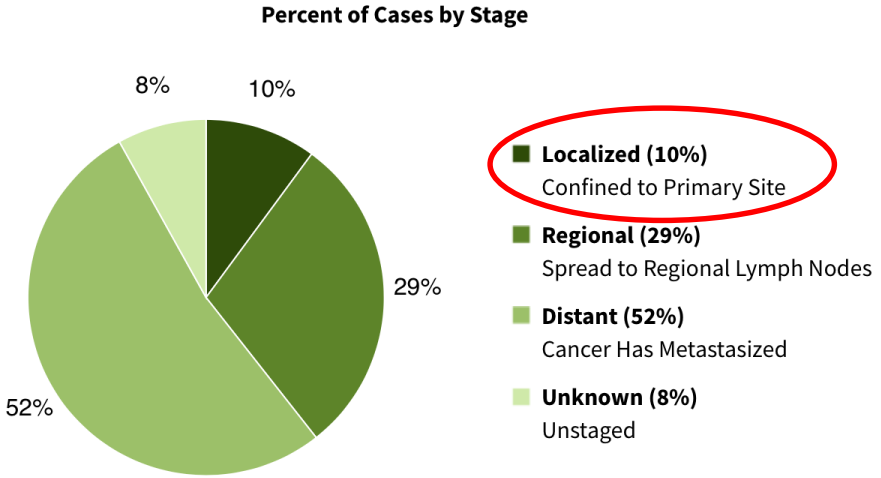
Estimated Deaths in 2019	45,750
% of All Cancer Deaths	7.5%

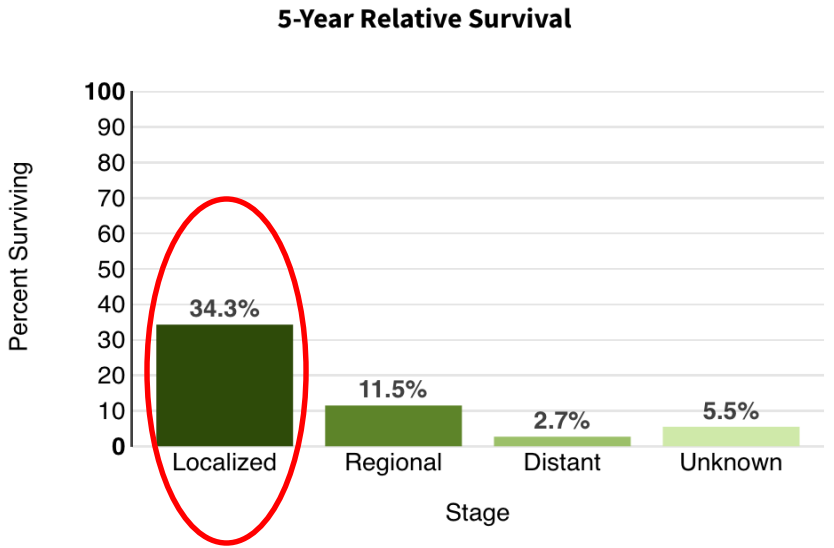
Percent Surviving 5 Years
9.3%
2009-2015



Data from the NIH/SEER program

WHY?





Data from the NIH/SEER program

Rationale for Neoadjuvant chemotherapy

1. Chemotherapy administered before surgery to non-dissected, well-oxygenated tissue may maximize any potential benefit compared to post op tissue
2. May decrease tumor volume, thus improving R0 resectability and completion of multimodal treatment
3. Minimize regional nodal disease/micrometastasis, hence reducing the risk of loco-regional recurrence.

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
- Identifying aggressive tumors; avoiding futile surgery

Data from AHN

- Argument for neoadjuvant chemotherapy for resectable pancreatic cancer
  - 70 PDA patients deemed resectable
  - 64 patients underwent surgery
    - 37 (58%) started adjuvant chemotherapy
    - Only 16 (25%) completed treatment.
    - Patients who completed their adjuvant chemotherapy had a significantly prolonged survival time versus those who did not complete all cycles (36.9 months vs. 18.8 months, *P* = 0.014).). Each additional cycle of chemotherapy conferred a relative survival advantage

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 were not included in survival analysis
  - Selection bias based on patient preference
  - Bias based on surgical team preference: location of tumor and ease of 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

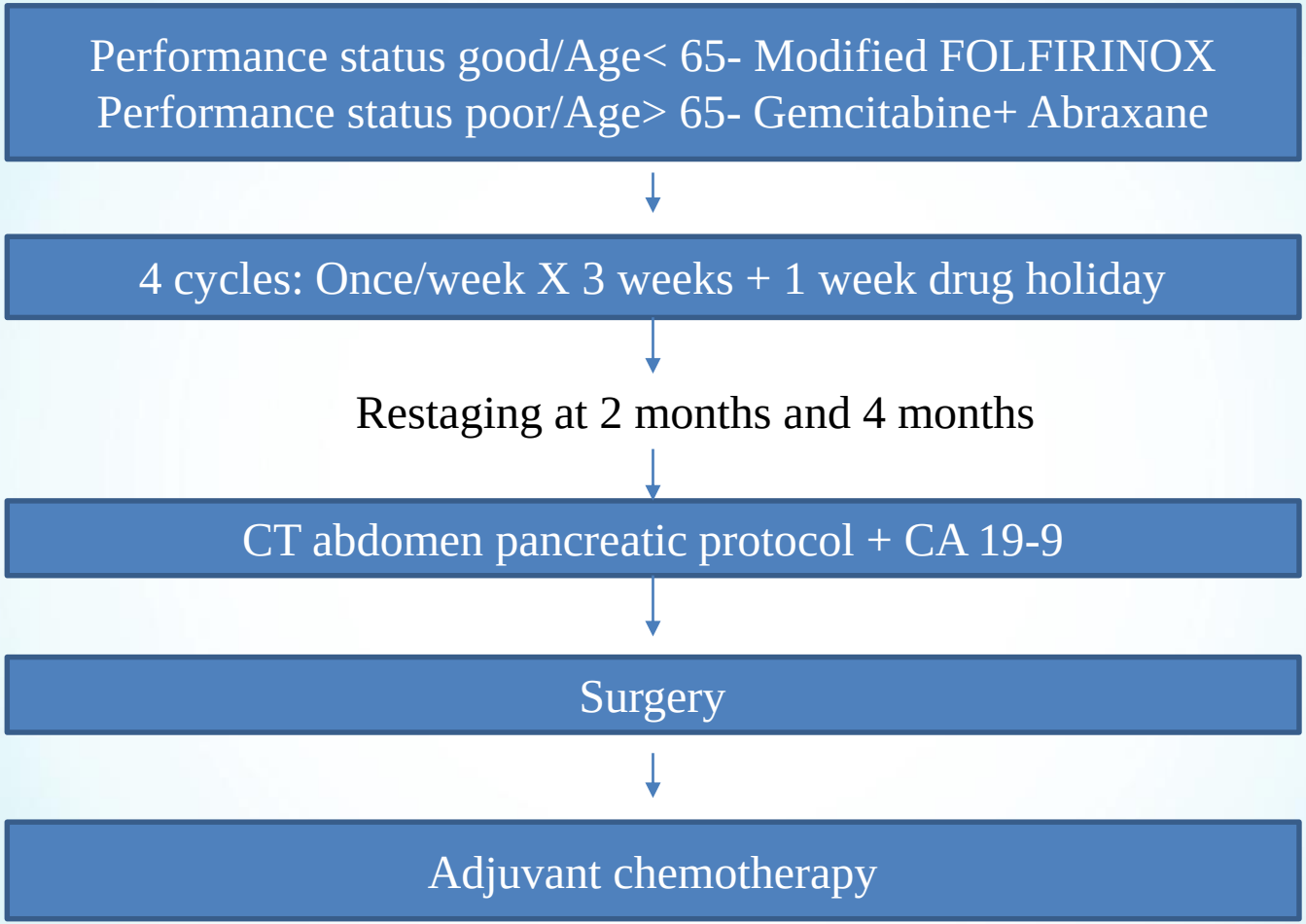
- Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - a national multicentre randomized controlled trial.
  - Panc head cancers only
  - Primary end point is overall mortality in patient who undergo resection
  - Secondary 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

- 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 Nov 2018 as a Quality improvement study


Performance status good/Age< 65- Modified FOLFIRINOX
Performance status poor/Age> 65- Gemcitabine+ Abraxane
4 cycles: Once/week X 3 weeks + 1 week drug holiday
Restaging at 2 months and 4 months
CT abdomen pancreatic protocol + CA 19-9
Surgery
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

- 9 resectable patients thus far
  - 3 patients received neoadjuvant therapy and underwent resection
  - 2 patients received neoadjuvant therapy and did not undergo resection
  - 4 patients are receiving neoadjuvant therapy and will probably undergo resection
  - 9/9 = 100% neoadjuvant therapy tolerance
  - 3/5 = 60% neoadjuvant therapy with successful resection
  - 3/3 = 100% R0 resection margin

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
- Schwatz 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.*
- Mokdad et al. Neoadjuvant Therapy Followed by Resection Versus Upfront Resection for Resectable Pancreatic Cancer: A Propensity Score Matched Analysis. *J Clin Oncol. 2017 Feb 10;35(5):515-522*
- Evans DB et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas**.** Arch Surg. 1992 Nov;127(11):1335-9
- Heinrich H et al. Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: results of a prospective phase II trial. Ann Surg. 2008 Dec;248(6):1014-22.
- Clyod JM et al.
Chemotherapy Versus Chemoradiation as Preoperative Therapy for Resectable PancreaticDuctal Adenocarcinoma: A Propensity Score Adjusted Analysis. Pancreas. 2019 Feb;48(2):216-222
- Bradley A et al. Upfront Surgery versus Neoadjuvant Therapy for Resectable Pancreatic Cancer: Systematic Review and Bayesian Network Meta-analysis. Sci Rep. 2019 Mar 13;9(1):4354.
- Ielpo, B. *et al*. Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. *Eur J Surg Oncol.* 42, 1394–1400 (2016).
- Roland, C. L. *et al*. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. *Annals of surgical oncology.* 22(4), 1168–1175 (2015).
- Tzeng, C. W. *et al*. Treatment sequencing for resectable pancreatic cancer: influence of early metastases and surgical complications on multimodality therapy completion and survival. *J Gastrointest Surg.* 18, 16–24 (2014).

Allegheny Health Network

Thank you