JOHNS HOPKINS
MEDICINE
RADIATION ONCOLOGY &
MOLECULAR RADIATION SCIENCES

“Ablative Radiation” for Locally Advanced Pancreatic Cancer

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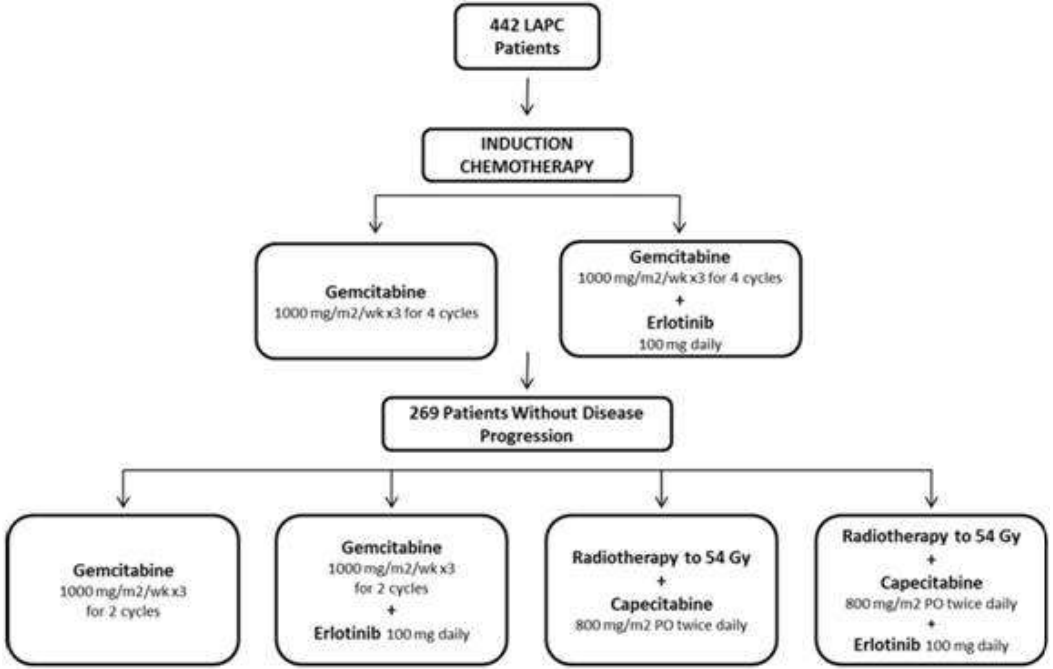
LAPC: value of local control

- Historically: LAPC = unresectable
  - In this setting, does radiation therapy add value beyond chemotherapy alone?

- Iacobuzio-Donahue et al., JCO 2009
  - Rapid autopsies performed in 76 pts who died of pancreatic cancer
  - Divergent extent of disease at autopsy
  - **30% w/ primarily locally destructive disease**
  - 70% w/ widespread metastasis
  - Potentially correlation with DPC4 status

- Additional series demonstrating potential for local morbidity/mortality
  - Cardillo et al., JNCCN, 2018
  - Sarkar et al., JNCCN, 2019

LAPC: LAP07

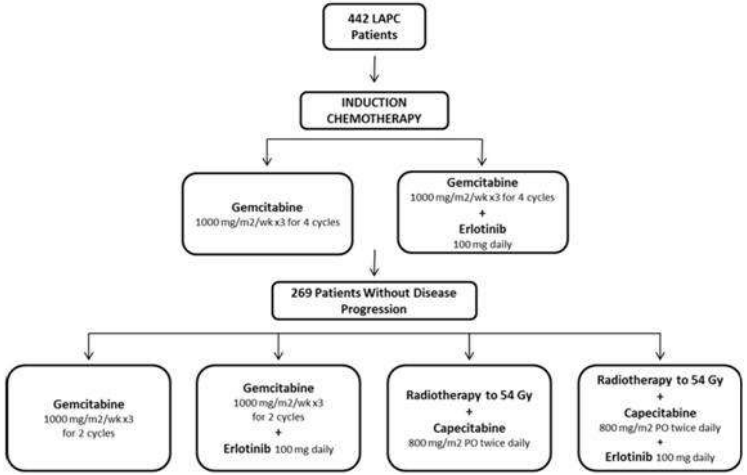


Hammel P, et al. JAMA. 2016;315:1844-1853.

LAPC: LAP07

- Negative study for OS
  - mOS: 15.2 vs. 16.5 mos, p=0.83

- But:
  - Chemo was gemcitabine alone
    - **Could RT be more helpful in setting of better systemic control?**
  - Improvement in local failure (32% vs 46%, p=0.04)
    - **Could more intensive RT further reduce likelihood of local failure?**
  - <5% surgically explored
    - **Could RT help with margin sterilization/ local recurrence risk reduction in setting of exploration?**



Hammel P, et al. JAMA. 2016;315:1844-1853.

LAPC: dose-escalated RT

- Treat to the tolerance of abutting duodenum and/or stomach
- PDAC dose prescriptions
  - Fractionated: 54 Gy in 30 fractions (**BED: 59 Gy**)
  - SBRT: 33 Gy in 5 fractions (**BED: 55 Gy**)

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right]$$

- Ablative RT experience for adenocarcinoma of the lung/liver
  - SBRT: 50 Gy in 5 fractions (**BED: 100 Gy**)
  - ~90% local control in these clinical scenarios

PDAC, Pancreatic adenocarcinoma; BED, biologically effective dose.

LAPC: dose-escalated RT

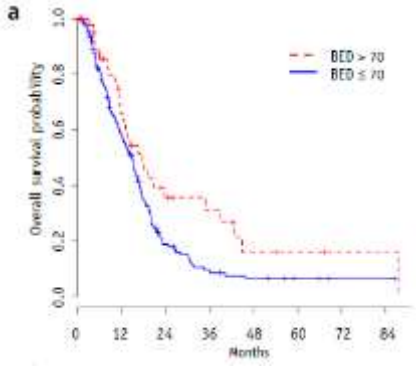
- Krishnan et al., IJROBP, 2016
  - LAPC patients treated with chemoRT at MDACC from 2006-2014
  - 47 patients with tumors >1cm from GI luminal structures (stomach, small bowel, or large bowel) were eligible for dose escalation
  - RT dose associated w/ improvement in local control and overall survival on multivariable analysis

- **Rare to have tumors >1cm from stomach, small bowel, and large bowel**

Table 1 Dose fractionation schedules, biologically effective dose, an

Dose and no. of fractions	Biologically effective dose (Gy)	No. of patients
63 Gy in 28 fx	77.2	14
70 Gy in 28 fx	87.5	11
67.5 Gy in 15 fx	97.9	7
60 Gy in 10 fx	96.0	1
50 Gy in 5 fx	100.0	1
51.3-70.4 Gy in 13-39 fx	70.4-84.3	13

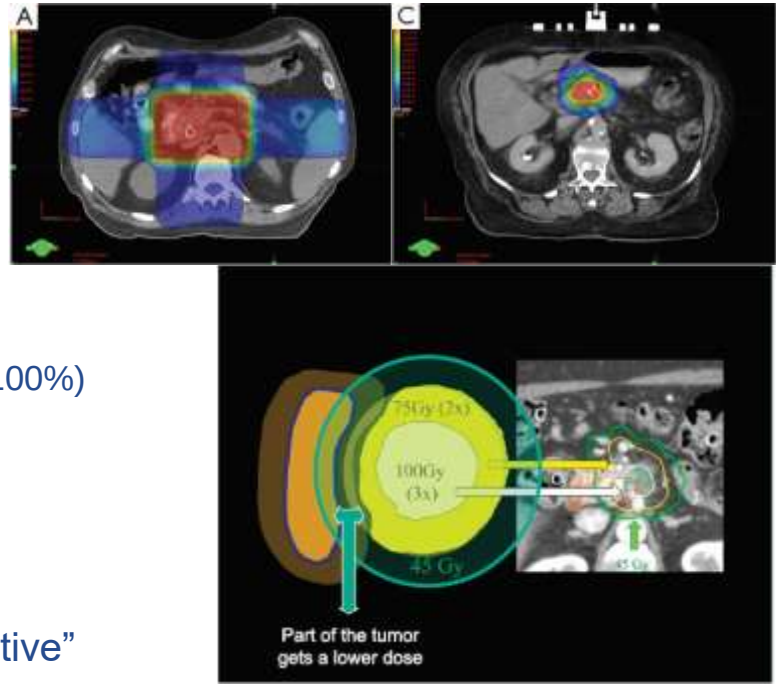
Abbreviations: fx = fractions; V50 = volume of organ receiving >50 Gy. α/β = 10 for calculation of biologically effective dose.



MDACC, MD Anderson Cancer Center.

LAPC: dose-escalated RT

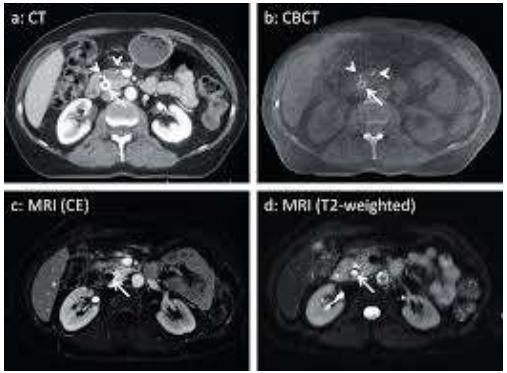
- Reyngold et al., JAMA Onc, 2021
  - MSKCC team decided to employ modern techniques to treat as much of the tumor as possible with “ablative” BED of 100 Gy
    - 75 Gy in 25 fxs
  - Tumor in close proximity to stomach/bowel structures was kept to conventional doses
  - Retrospective report of 119 patients
    - Tumor coverage by BED of 100 Gy: 76% (16-100%)
    - mOS: 27 mos from diagnosis
    - 2-yr OS: 38%
    - 2-yr loco-regional failure of 32.8%
- Is this truly ablative RT?
  - Probably best characterized as “partially ablative”



MSKCC, Memorial Sloan Kettering Cancer Center.

MR-guided radiation therapy

- Technical challenges with targeting pancreatic cancer with radiation therapy
  - Motion of tumor with respiration and variation in anatomy with changing bowel gas patterns
  - Inter-fraction (i.e. between treatment) variation in anatomy
    - CT-based solution: fiducial alignment, larger margins
    - MR-guided solution: adaptive planning based on daily anatomy
  - Intra-fraction (i.e. during treatment) variation in anatomy
    - CT-based solution: fiducial alignment based on interval CTs during treatment
    - MRI-guided solution: real-time direct tumor tracking
- Stereotactic MR-guided Adaptive Radiation Therapy (SMART)



SMART

- SMART trial
  - Multi-institutional, prospective study with 136 patients across 13 centers
  - Patients with BRPC or LAPC s/p 3 months of multi-agent chemo and with CA19-9 ≤ 500 after chemo
  - SBRT to 50 Gy in 5 fractions using MR-guidance
  - Primary endpoint
    - Rate of ≥3 acute toxicity definitely related to RT
      - Goal to reduce from historical estimate of 15.8% to 8%
  - Surgical exploration allowed after SBRT at treating team's discretion

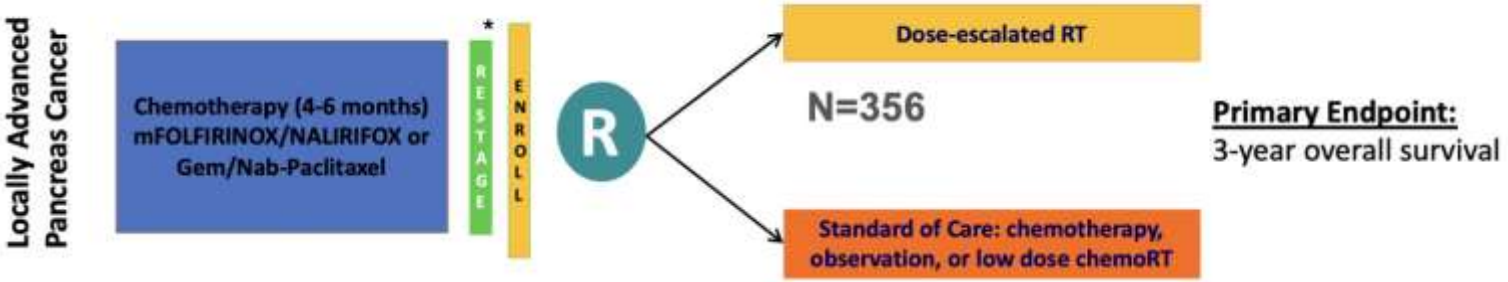
SMART

- Parikh et al., IJROBP, 2023
  - Primary endpoint met: no patients with acute toxicity definitely related to RT
  - Tumor coverage by ablative dose: 86% (30-100%)
    - **MR-guided RT solves many technical challenges but does not change the fact that the proximity of pancreatic tumors to the stomach or duodenum**
    - **MR-guided RT probably still best characterized as “partially ablative”**

- Chuong et al., Radiother Oncol, 2024
  - Longer-term outcomes
    - mOS: 22.8 mos
    - 2-yr OS: 53.6%
    - 2-yr LC for resected vs unresected patients
      - 90% vs 71%, p=0.019
    - Of 44 pts whom underwent resection, 3 incidences of post-operative mortality (7%) related to vascular complications

Planned NRG study

NRG GI-011: A Phase III Randomized Trial of Dose Escalated Radiation in Locally Advanced Pancreas Cancer Patients (LAP100)



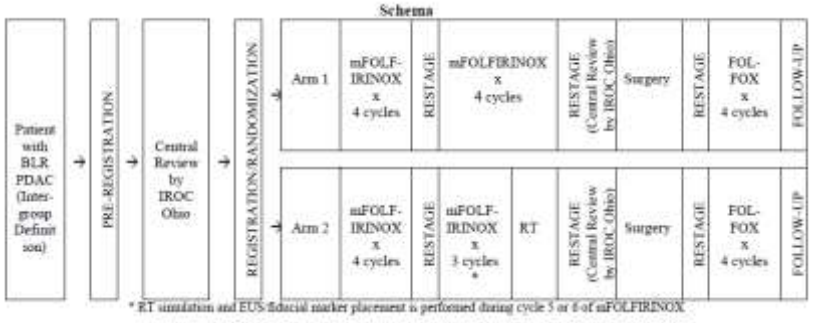
LAPC: JHH surgery outcomes

- Gemenetzis et al., Ann Surg, 2019
  - 461 LAPC pts seen through our pancreatic multidisciplinary clinic from 2013-2017
  - 116 (28%) LAPC pts deemed eligible for surgical exploration after upfront therapy
    - 96% received RT prior to exploration
    - 70% (20% of total cohort) successfully underwent resection
    - 90% R0 resection rate
  - mOS: 35.3 mos in resected pts vs. 16.3 mos in unresected pts
- NCT02648282 (unpublished data)
  - Study of IO + SBRT after > 4mos of induction chemo
  - 44% underwent resection with ~90% R0 resection rate
- Is there value to pre-op RT in this setting?

SBRT, stereotactic body radiation therapy

Pre-op RT: Alliance study

- Alliance study (A021501)
  - Randomized phase II study exploring neoadjuvant mFFX +/- RT
  - RT technique was SBRT
    - Dose: 6.6 Gy x 5 (similar biologic dose to 50.4 Gy in 28 fxs)
  - Primary endpoint 18-month OS
    - Null hypothesis: 18-month OS of 50%
    - Alternative hypothesis: 18-month OS of 63%
    - "Pick the winner" design with comparison of two arms if both arms met alternative hypothesis
    - Interim closure of either arm if ≤11 of first 30 pts in either arm achieved R0 resection



mFFX, modified FOLFIRINOX.

Katz MHG, et al. JAMA Oncol. 2022;8:1263-1270.

Pre-op RT: Alliance study

- Katz et al., JAMA Onc, 2022
  - 126 patients enrolled across **50 sites**
  - RT arm closed early due to meeting futility definition
  - Primary endpoint 18-month OS
    - mFFX alone: 67.9%
    - mFFX/SBRT: 47.3%
  - Conclusions (from the paper)
    - Neoadjuvant mFFX can be considered a reference standard for future studies
    - Unclear role for RT

	Arm A (mFOLFIRINOX) n = 70	Arm B (mFOLFIRINOX + RT) n = 56
Initiated preop treatment	66	55
Started cycle 8 ctx or RT*	47 (71)	40 (73)
Surgery	38 (58)	28 (51)
Pancreatectomy	32 (48)	19 (35)
R0 pancreatectomy	28 (42)	14 (25)
Initiated postop ctx	22 (33)	13 (24)
Completed all treatment	20 (30)	10 (18)

Ctx, chemotherapy

Pre-op RT: JHH experience

- Johns Hopkins experience (2016-2019)

	JHH BRPC	Alliance
Number of pts	64	40
Number of pts explored	58 (91%)	28 (70%)
Number of pts not explored due to:		
- Metastatic disease	3	?
- Local extent	2	?
- Medical reasons	1	?
Number of pts resected	50 (78%)	19 (48%)
Number of pts not resected due to:		
- Intra-op metastatic disease	7	?
- Intra-op local extent	1	?
Number of pts w/ R0 resection		
- Resected patients	48/50 (96%)	14/19 (74%)
- All patients	48/64 (75%)	14/40 (35%)

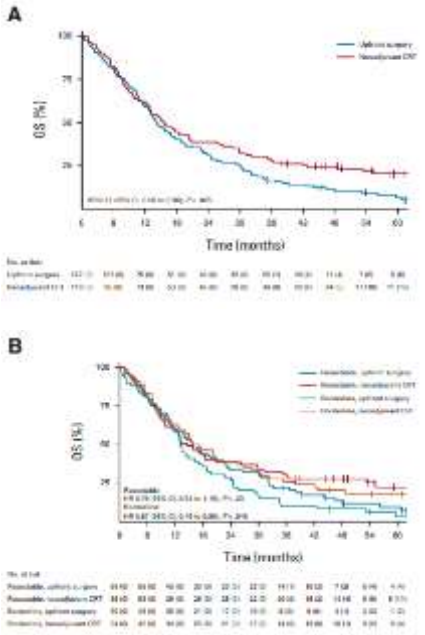
Hill et al., Cancer Med, 2022

Pre-op RT: PREOPANC

- PREOPANC (Versteijne et al., JCO, 2022)
  - 246 BR (46%) or resectable (54%) patients
  - Randomized to upfront surgery
    - Upfront surgery → adjuvant gemcitabine (6 cycles)
    - Gem-based RT → surgery → adjuvant gemcitabine (4 cycles)
      - Cycle of gemcitabine before, concurrent with, and after RT
      - RT dose: 2.4 Gy x 15
      - RT volume
        - » No elective treatment but larger margins compared to Alliance SBRT study
  - Primary endpoint OS

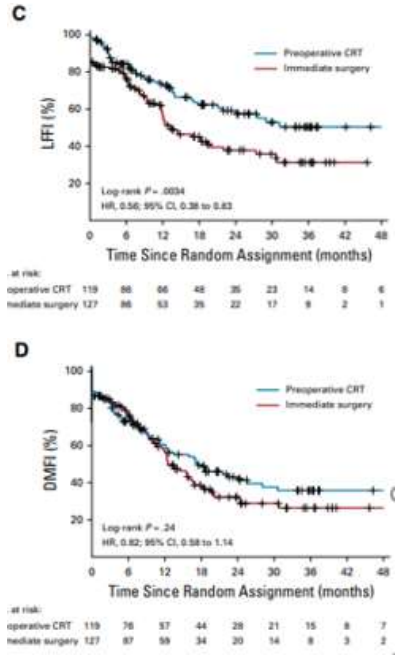
Pre-op RT: PREOPANC

- PREOPANC (Versteijne et al., JCO, 2022)
  - Median f/u 56 mos
  - Improved OS
    - mOS: 15.7 vs. 14.3 mos (p=0.025)
    - 3-yr OS: 27.7% vs. 16.5%
    - 5-yr OS: 20.5% vs. 6.5%
    - 5-yr OS in patients resected and who received adjuvant chemo
      - 31.2% vs. 10%
  - OS hazard ratios by stage
    - Resectable: 0.79 (0.54 – 1.16)
    - BR: 0.67 (0.45 – 0.99)



Pre-op RT: PREOPANC

- PREOPANC (Versteijne et al., JCO, 2022)
  - Disease-free survival
    - HR:0.69; 95% CI: 0.53 to 0.90, p=0.009
  - Loco-regional failure-free survival
    - HR:0.57; 95% CI: 0.39 to 0.83, p=0.004
  - Distant metastasis-free survival
    - HR:0.74; 95% CI, 0.54 to 1.03, p=0.07



Pre-op RT: JHH experience

- High local failure rates despite high R0 resection rate
  - 155 BR/LA patients treated with SBRT from 2016-2019
    - 6.6 Gy x 5 targeting gross disease + involved vasculature (similar to A021501)
  - 85% explored, **92% R0 resections**

	LAPC	BRPC	All patients
Number of patients, *N*	91	64	155
Surgically explored, *N* (%)	74 (81)	58 (91)	132 (85)
Not surgically explored due to:			
Metastatic disease	5	3	8
Local extent	8	2	10
Medical reasons	4	1	5
Successfully resected, *N* (%)	57 (63)	50 (78)	107 (69)
Surgery aborted due to:			
Intra-Op. metastatic disease	11	7	18
Intra-Op. local extent	4	1	5
Intra-Op. fibrosis	2	0	2
Number of patients with R0 resection, *N* (%)			
All patients	50/91 (55%)	48/64 (75%)	98/155 (63%)
Resected patients	50/57 (88%)	48/50 (96%)	98/107 (92%)

Hill et al., Cancer Med, 2022

Pre-op RT: JHH experience

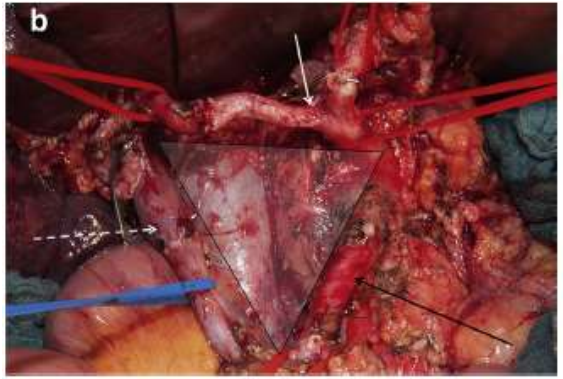
- High local failure rates despite high R0 resection rate
  - 155 BR/LA patients treated with SBRT from 2016-2019
    - 6.6 Gy x 5 targeting gross disease + involved vasculature (similar to A021501)
  - 85% explored, **92% R0 resections**
  - Of resected patients
    - **>40% local failure rate**

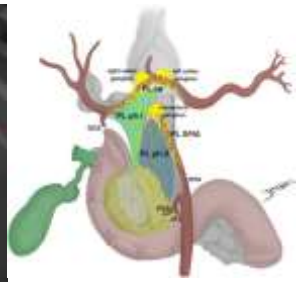
- **How can we achieve more durable local control?**
  - **RT field design**
  - **RT dose**

Hill et al., Cancer Med, 2022

RT field design: the “Triangle”

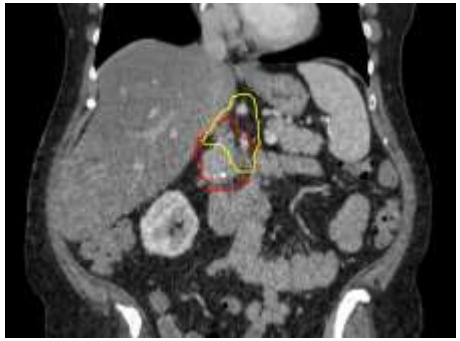
- Hackert et al., HPB, 2017
  - “Heidelberg Triangle”
  - Space between celiac, CHA, SMA, & PV/SMV
  - Enriched in extra-pancreatic perineural tracts at risk of harboring un-dissected microscopic residual disease after chemo, which may mediate local failure
    - Pancreatic head plexi 1 & 2
    - Celiac, SMA, and CHA plexi
- Hill et al., Pract Radiat Oncol, 2022
  - JHH patterns of local failure
  - >90% of local failures map to the Triangle

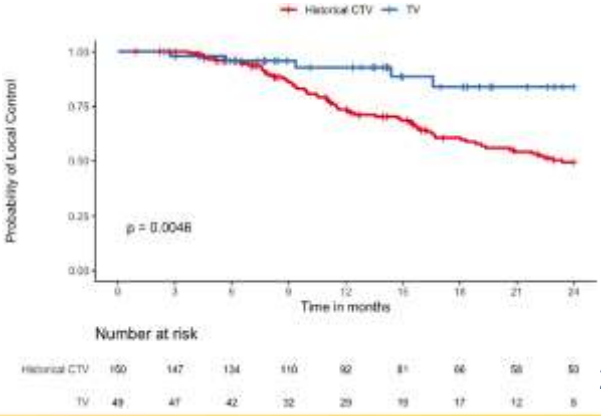




RT field design: the “Triangle”

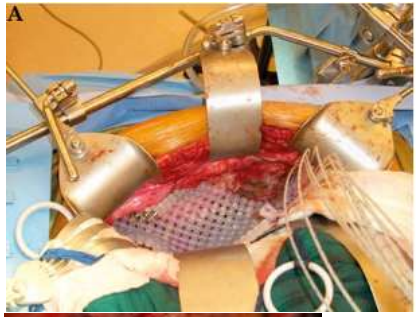
- At the end of 2020, pre-operative SBRT target volume was modified at JHH to include the “Triangle”
- Mao et al., ASTRO, 2023
  - Decrease in 2-yr local failure from >40% to <20%
  - Treatment of the Triangle was most important predictor of LC on MV analysis
- How can we further improve local control?

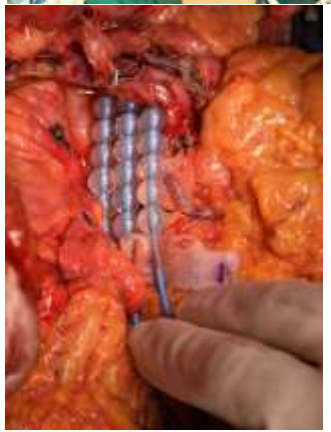




RT dose: IORT

- **Can the addition of IORT to the Triangle after pre-op RT help further reduce local recurrence?**
- Rationale
  - Duodenum removed during Whipple surgery
  - Stomach and rest of the bowel can be shielded
  - Direct access to the Triangle
  - Peri-pancreatic vasculature and nerves become the dose-limiting structures, but RT tolerance of these structures are high
- NCT05141513: “A safety study of IORT following SBRT in the treatment of localized pancreatic adenocarcinoma”
  - Pre-op SBRT to the Triangle 8 Gy x 5
  - IORT to the Triangle 15 Gy x 1
  - Cumulative BED (109 Gy)





IORT, intraoperative radiation therapy.

Conclusions

- In the unresectable setting, delivery of “ablative” doses of radiation appears to increase local control, which is an important endpoint for improving both quality and quantity of life
- However, full ablation of the entire tumor with radiation is rarely achievable
- As such, surgical resection should be pursued when technically feasible and in the right patient
- In the setting of surgery, pre-operative radiation can help reduce local recurrence
- Importantly, elective targeting of the “Triangle” should be part of the pre-operative radiation approach
- Intra-operative radiation therapy may also offer an opportunity to escalate dose to “ablative” levels to the Triangle to further help minimize local recurrence rates after surgery and is the subject of ongoing investigation

Thank you!