The Role of Radiation Therapy in Pancreatic Cancer

October 25, 2019

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The Role of Radiation in Pancreatic Cancer

Pancreatic Cancer Action Network Webinar
October 29, 2019

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MD Anderson Cancer Center

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DISCLOSURES

- Research Support: Oncosil, Galera, and Augmenix, RaySearch.
- Consultant: BTG, Celgene, Sirtex, Medtronic, boston scientific

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Outline: Role of Radiation Therapy in PCA

1. Anatomy
2. Staging
3. RT advances
4. Resectable (Adjuvant and Neoadjuvant)
5. Borderline Resectable
6. Unresectable/ Locally Advanced
7. Recurrent
8. Metastatic

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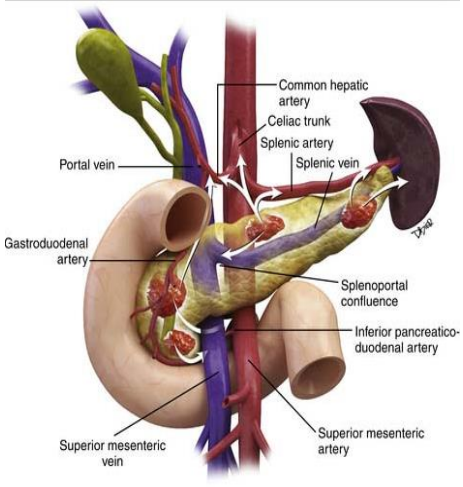
ANATOMY



- Where is my pancreas?
- Where is my tumor?
- Vessel review

Netter textbook

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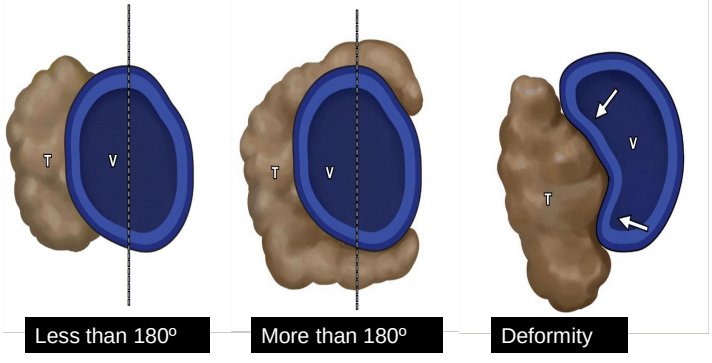
Resectability: Contact with Veins



** Veins can be reconstructed

Slide(s) courtesy of Dr. Mahmoud Al-Hawary

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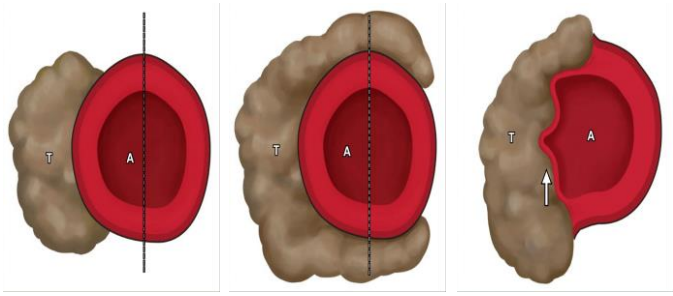
Resectability: Contact with Arteries

Assessment based on:

- Degree of tumor contact with the vessel circumference
- Whether vessel caliber narrowing or contour deformity is present



Less than 180º | More than 180º | Deformity

Difficult to resect arteries

Slide(s) courtesy of
Dr. Mahmoud Al-Hawary

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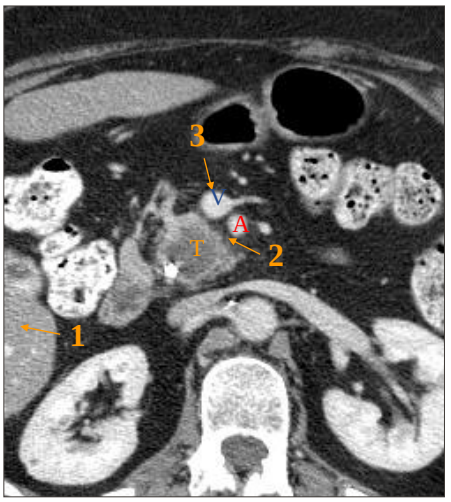
What stage am I?

1. Resectable
2. Borderline Resectable
3. Unresectable or Locally Advanced

4. Metastatic (tumor spread beyond the pancreas and to another location)

Prospective Identification of Anatomically Resectable Pancreatic Cancer by CT Scan

1. Absence of disease outside of the pancreas
2. Tissue plane between tumor and SMA/CA
3. Open SMV-PV confluence



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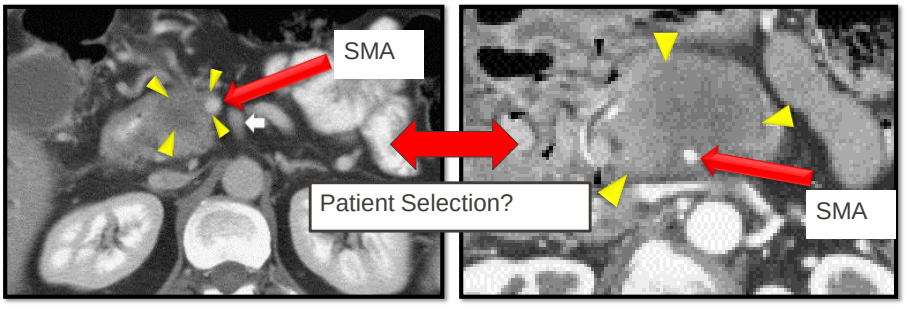
Borderline Resectable and Locally Advanced Pancreatic Cancer

Borderline Resectable

Locally Advanced (Unresectable)



- Tumor ***abuts*** a major blood vessel(s)
- Deemed resectable
- Neoadjuvant therapy recommended

- Tumor ***encases*** a major blood vessel(s)
- Deemed unresectable or LAPC
- New role for "definitive therapy"

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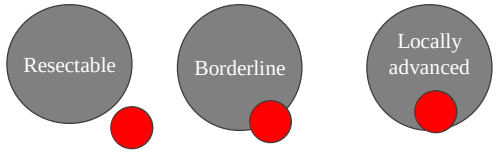
Resection Determined by Vessel Involvement



AHPBA/SSO/SSAT/NCCN			
	Resectable	**Borderline**	**Locally Advanced**
Superior mesenteric or Portal vein	No contact	Abut, encase or occlude	Not reconstructable
Superior mesenteric artery	No contact	Abut	Encased
Common Hepatic artery	No contact	Abut or short-segment encase	Long-segment encase
Celiac Trunk	No contact	<180	>180

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Pancreatic Cancer

2019 estimated 56,770 pancreas cancer dx in US

45,750 deaths from pancreas cancer

Surgery is the only potentially curative option

- 5-year survival: 10-25%
  - Resected: ~2 years median overall survival (OS)
  - Borderline resectable: ~1-2 years median OS
    - Improved with surgery, margins improved with radiation therapy (RT)
  - Unresectable/Locally advanced (palliative): ~1 year median OS (now better)

Siegel Ca Cancer J Clin 2019

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Multidisciplinary Teams

Present cases using outline	Review pathology	Review imaging CT/PET/MRI/ EUS	Discuss case and reach consensus	See patients and discuss options	Enroll in trials Dictate note and cc to referring physicians

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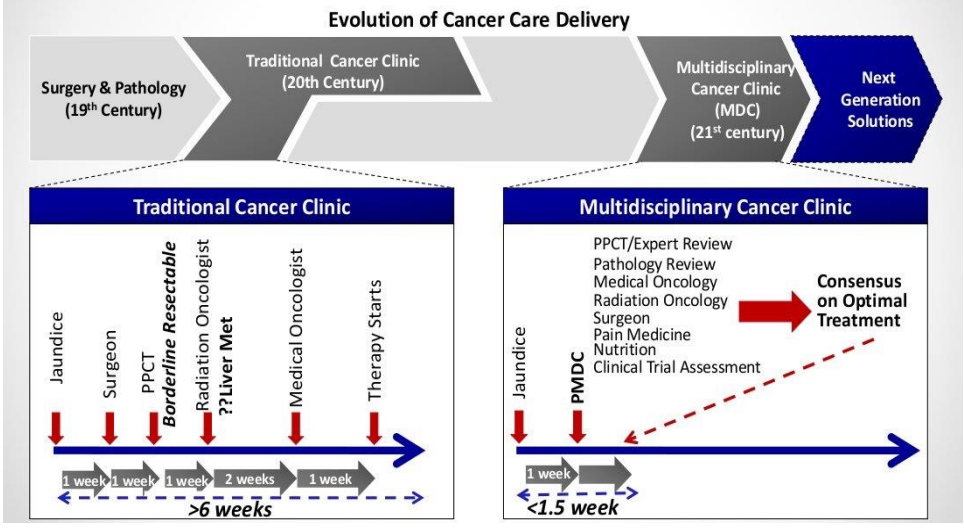
Traditional vs. Multidisciplinary Evaluations



Role of radiation therapy in pancreas cancer

Adjuvant: After surgery, RT given in node and/or margin positive resections. Role of intraoperative radiation therapy.

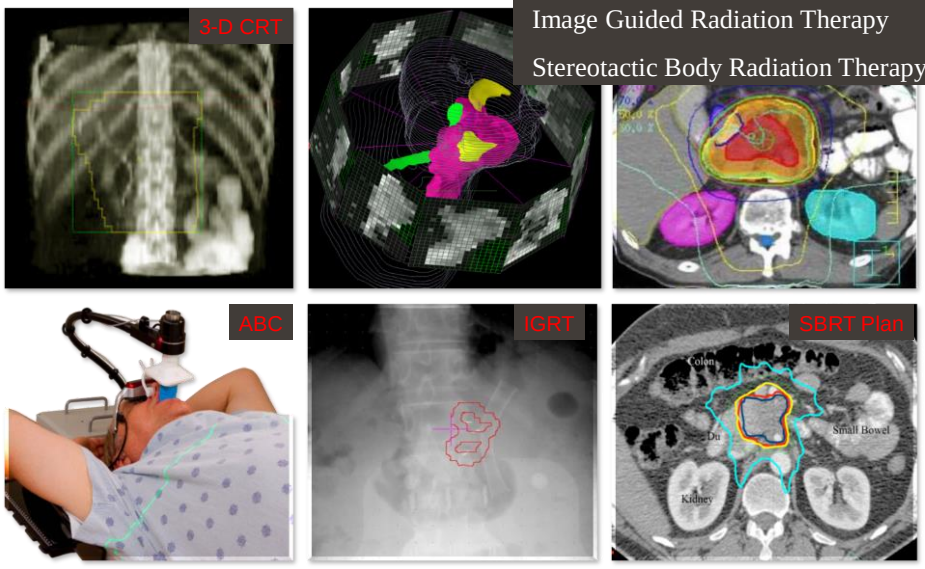
Neoadjuvant: Given in potentially resectable pancreas cancer. Usually between chemotherapy and surgery.

Definitive: Not surgical. Goal is to prolong life and balance quality of life.

Oligometastatic: Given to 1-5 metastatic tumors in very select cases after maximal therapy (controversial).

Evolution of Radia

3-D Conformal radiation therapy
Intensity modulated radiation therapy
Active Breathing Control
Image Guided Radiation Therapy
Stereotactic Body Radiation Therapy



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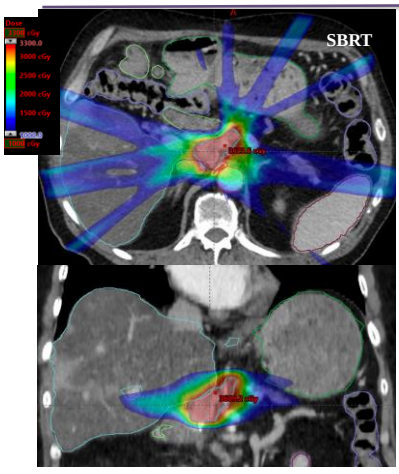
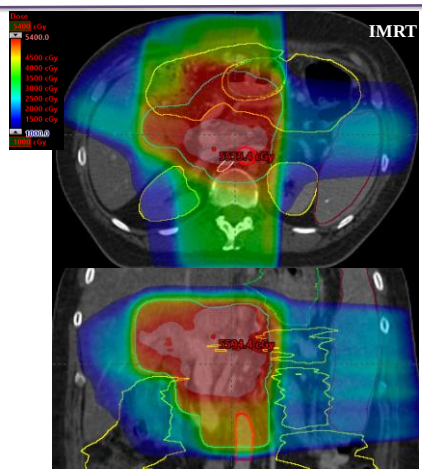
What approach with RT is optimal for PCA? Typical dose distribution for SBRT vs conventional IMRT





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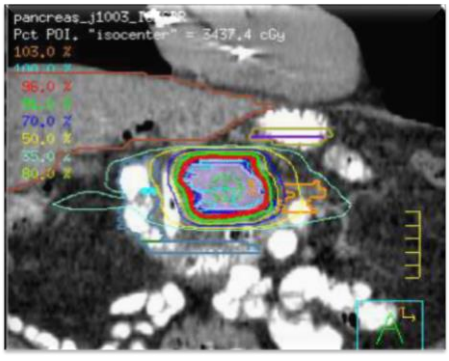
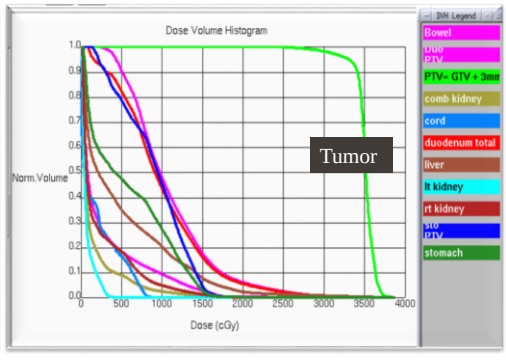
SBRT Planning & Delivery



Treatment Plan
(5-6.6 Gy x 5 fractions)



SBRT Dose Volume Histogram

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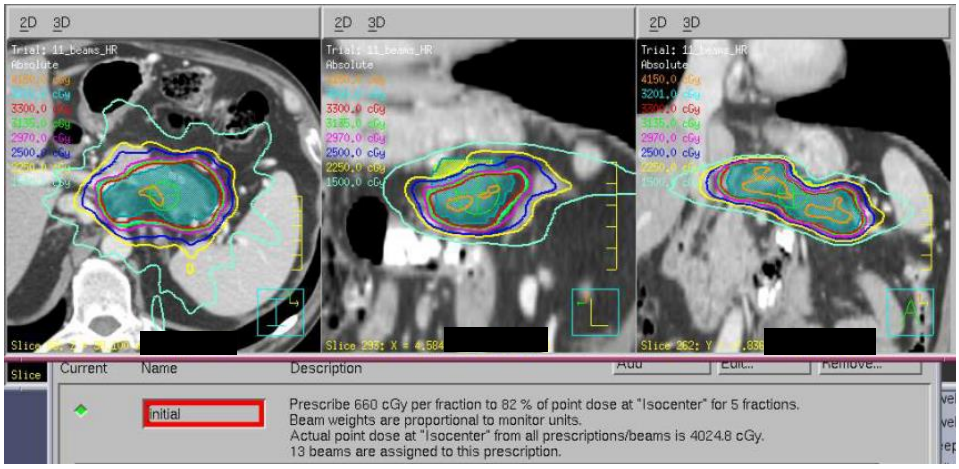
Body/Tail Example



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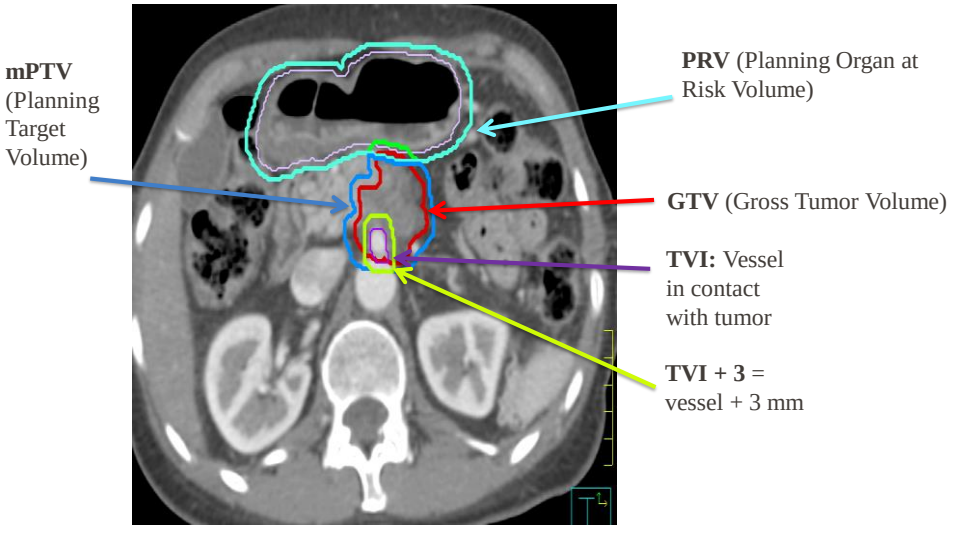

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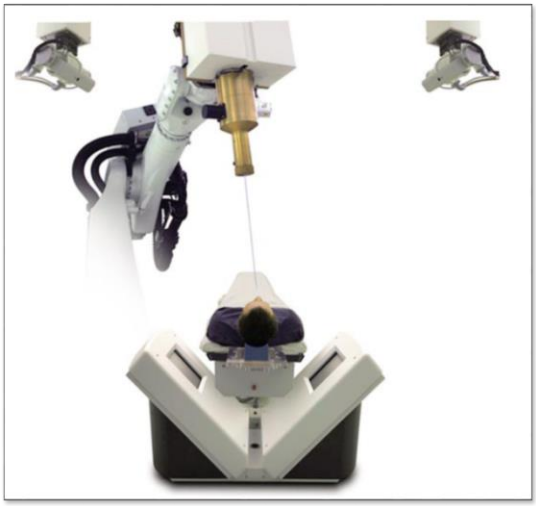
Modern SBRT Treatment Devices



CYBERKNIFE

TRILOGY

SYNERGY

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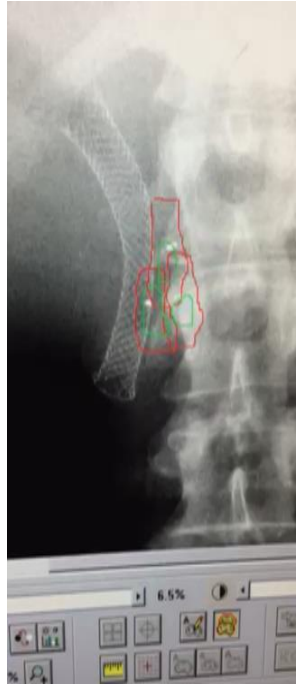
Free-Breathing Fiducial



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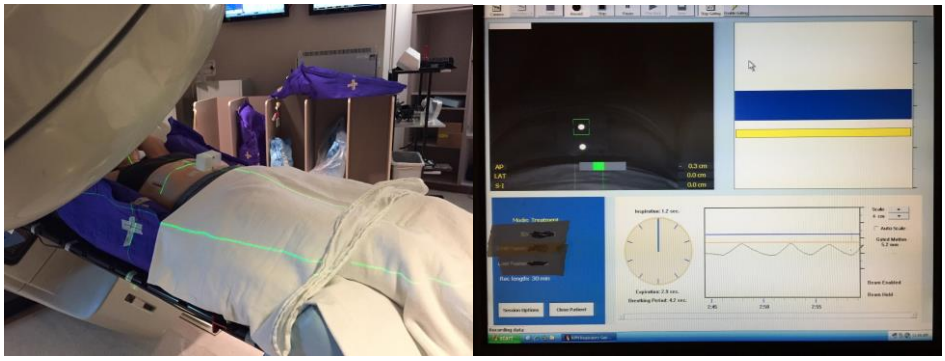
Breath Hold CT on Rails with tracking



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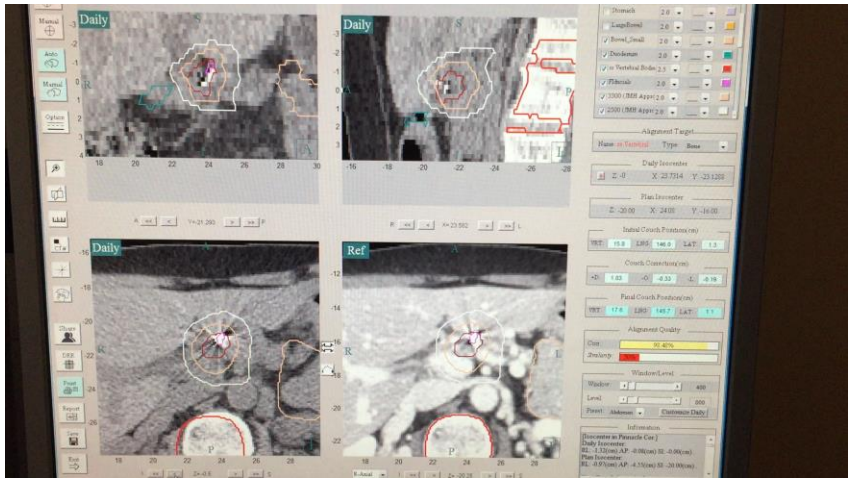
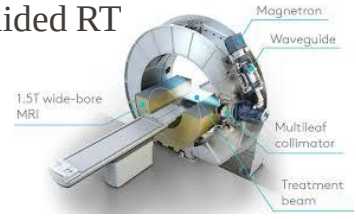
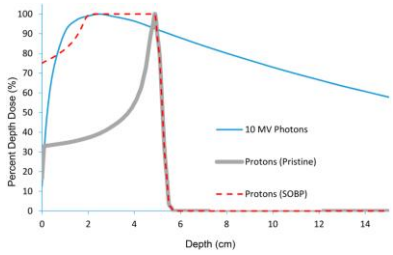
Breath Hold Video CT on Rails with Fiducials

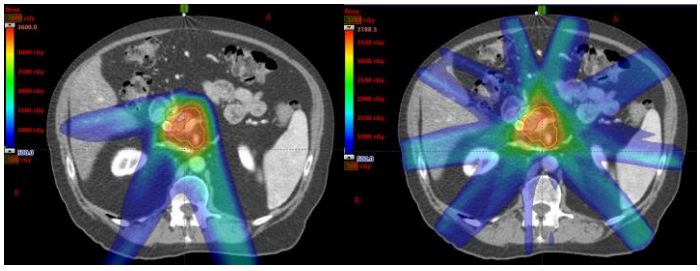


MR guided RT

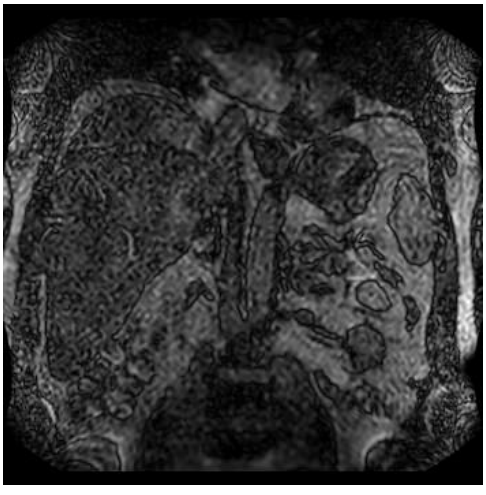


SBPT (PROTON)





MR guided RT



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SBRT (hypofractionated) vs. Standard RT

- Achieve sharper dose fall-off gradients to normal tissue
- Less acute toxicity, short course (< 1 week)
- Can be combined with other modalities
- Quality of life (1 week)
- Less lymphopenia
- Radiobiology more favorable?
- Anatomy may preclude ability to deliver full dose
- Higher late toxicity?
- Smaller fields?

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Original Article

Phase 2 Multi-institutional Trial Evaluating Gemcitabine and Stereotactic Body Radiotherapy for Patients With Locally Advanced Unresectable Pancreatic Adenocarcinoma

Joseph M. Herman, MD[1]; Daniel T. Chang, MD[2]; Karyn A. Goodman, MD[3]; Avani S. Dholakia, MD[1]; Siva P. Raman, MD[4]; Amy Hacker-Prietz, PA-C[1]; Christine A. Iacobuzio-Donahue, MD[5]; Mary E. Griffith, RN[1]; Timothy M. Pawlik, MD[6]; Jonathan S. Pai, BA[2]; Eileen O'Reilly, MD[7]; George A. Fisher, MD[8]; Aaron T. Wild, MD[1]; Lauren M. Rosati, BS[1]; Lei Zheng, MD[9]; Christopher L. Wolfgang, MD[6]; Daniel A. Laheru, MD[9]; Laurie A. Columbo, RN[2]; Elizabeth A. Sugar, PhD[10]; and Albert C. Koong, MD, PhD[2]

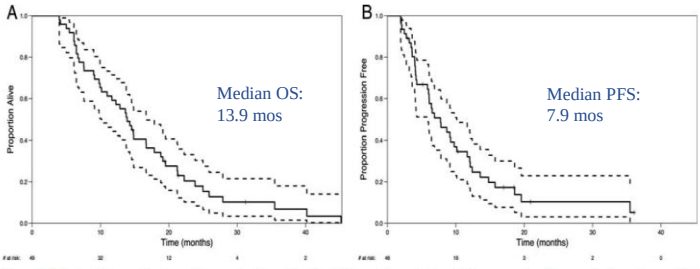

Figure 2. Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.

Herman JM et al. Cancer 2015

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Phase II Multi-institutional Trial: SBRT Toxicity and QOL

Toxicity

- Acute GI
  - Grade 2: **0%**
  - Grade ≥3: **12.2%**
- Late GI
  - Grade 2: **2.1%**
    - Enteritis
  - Grade ≥3: **8.5%**
    - Fistula (1)
    - Ulcer (3)

Quality of Life (EORTC)

- Mean global QOL:
  - Scores unchanged pre/post SBRT

Surgery

- 5 (10%) were deemed resectable after therapy
  - 1 (2%) denied surgery
  - The remaining 4 (8%) patients underwent margin- and node-negative resection

➡ LAPC patients may successfully be resected?!

Herman JM et al. Cancer 2015

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SBRT vs. CFRT Outcomes

Outcomes for Patients With Locally Advanced Pancreatic Adenocarcinoma Treated With Stereotactic Body Radiation Therapy Versus Conventionally Fractionated Radiation

Jim Zhong, MD[1,2]; Kirtesh Patel, MD[1,2]; Jeffrey Switchenko, PhD[2,3]; Richard J. Cassidy, MD[1,2]; William A. Hall, MD[4]; Theresa Gillespie, PhD[2,5]; Pretesh R. Patel, MD[1,2]; David Kooby, MD[2,5]; and Jerome Landry, MD[1,2]

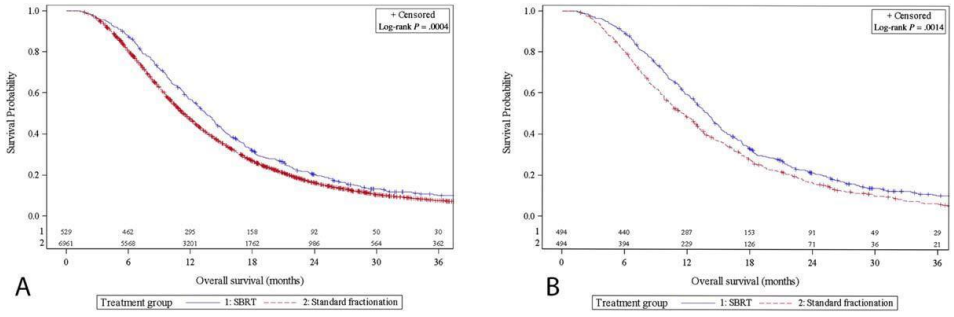
National Cancer Data Base (NCDB)

cT2-4/N0-1/M0 adenocarcinoma of the pancreas diagnosed from 2004 to 2013 were analyzed

Among 8450 patients, 7819 (92.5%) were treated with CFRT, and 631 (7.5%) underwent SBRT.

Radiation therapy delivered at **≤ 2 Gy was deemed CFRT**, and radiation therapy delivered at **≥ 4 Gy per fraction** was considered **SBRT**.

SBRT (5 days) vs. Chemoradiation Outcomes



CONCLUSIONS: SBRT was associated with **superior OS** in comparison with CFRT for LAPC, and these findings remained significant in a propensity-matched analysis.

Prospective SBRT Pancreas Trials: Mostly LAPC

Table 1 Prospective studies of stereotactic body radiation therapy for pancreatic cancer

Study	Regimen	Patients (n)	1-year local control (%)	Median OS (months)	Acute toxicity grade 3+ (%)	Late toxicity grade 2+ (%)
Koong et al[10]	15–25 Gy/1 fx	15 LA or LR	100	11	0	NR
Koong et al[11]	45 Gy IMRT +5-FU → 25 Gy/1 fx	16 LA	94	8.3	13	NR
Høyer et al[16]	15 Gy ×3	22 LA	57	5.4	79 grade 2+	94
Schellenberg et al[12]	Gemcitabine → 25 Gy/1 fx → gemcitabine	16 LA	100	11.4	6	47
Polistina et al[17]	10 Gy ×3	23 LA	50	10.6	0	0
Schellenberg et al[13]	Gemcitabine → 25 Gy/1 fx → gemcitabine	20 LA	94	11.8	5	20
Tozzi et al[46]	Gemcitabine → 45 Gy/6 fx or 36 Gy/6 fx	30 LA or LR	77	11	0	0
Gurka et al[18]	Gemcitabine → 25 Gy/5 fx → gemcitabine	10 LA	40	12.2	0	0
Herman et al[19]	Gemcitabine → 33 Gy/5 fx	49 LA	78	13.9	12	11

Note: Arrows demonstrate sequence of the treatment regimen.
Abbreviations: 5-FU, 5-fluorouracil; fx, fraction; Gy, gray; IMRT, intensity modulated radiotherapy; LA, locally advanced; LR, locally recurrent; NR, not reported; OS, overall survival.

Hong...Palta. Oncotargets and Therapy 2016

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Pancreas Cancer Treatment Strategies

Resectable

- Surgery → chemo
- Surgery → chemo → chemo/RT
- Chemo → Surgery → chemo
- **Chemo → +/- RT → surgery**

Borderline Resectable

- Chemo → surgery??
- Chemo/RT → surgery??
- **Chemo → +/- RT → surgery**

Locally Advanced

- Chemo
- Chemo/RT
- Chemo → chemo/RT
- **Chemo → +/-RT → surgery??**

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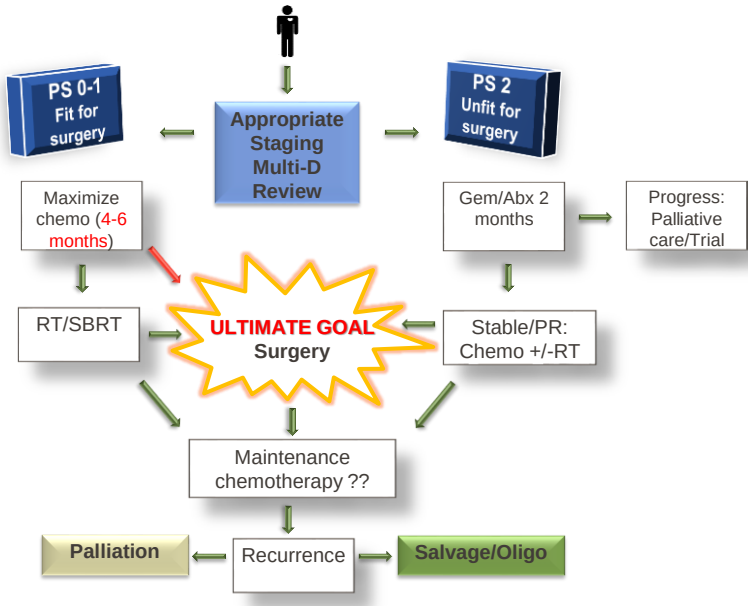
Localized pancreas cancer



Resectable Disease: Adjuvant/Neoadjuvant

Role of Radiation after Surgery: Margin-Positive= Poor Survival

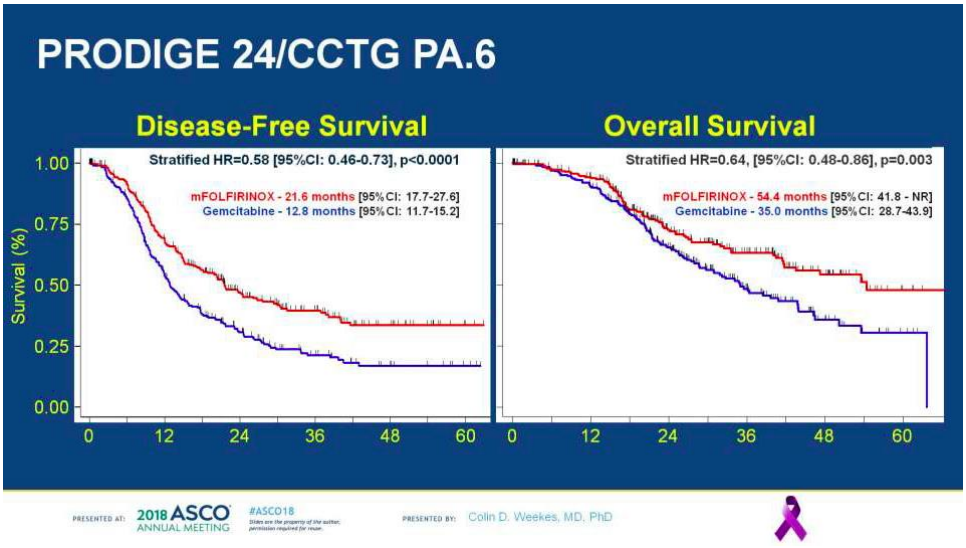
Institution	Margin + Resection Rate	Median OS (R2)	Median OS (R1)	Median OS (R0)
Mayo Clinic[1]	24%	10	15	18-19
Hopkins[2]	42%	--	14	20
MGH[3]	30%	11	15	22

[1]Fatima J et a, Arch Surg, 2010
[2]Winter JM et al, J Gastrointest Surg, 2006
[3]Konstandinidis et al, GI ASCO 2010

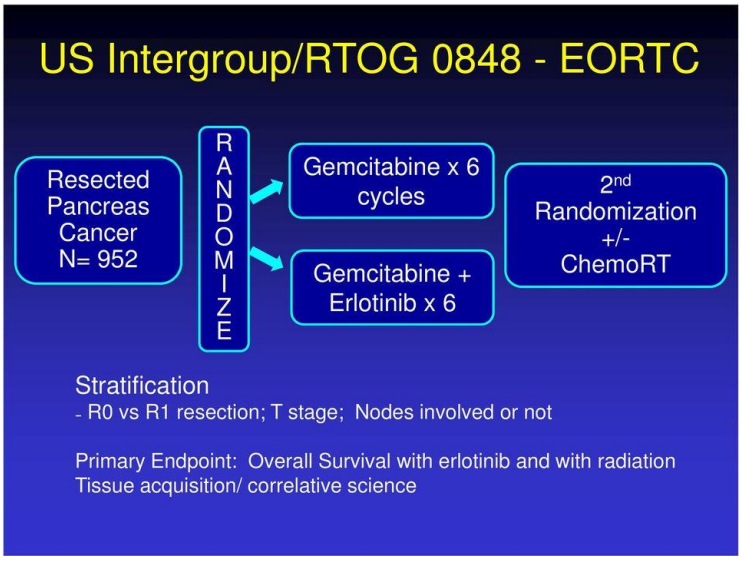
Goal of radiation is to achieve a MARGIN-NEGATIVE (R0) resection

Table courtesy of Dr. Christopher Crane (MDACC)

Adjuvant Chemotherapy



Adjuvant Chemotherapy +/- Radiation Therapy



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Adjuvant Radiation Therapy

Standard dose chemoradiation (5-6 weeks):

- Duration of systemic chemotherapy is limited
- Is unlikely to sterilize positive margins
- Role is controversial (RTOG 0848)

Local progression is common:

- At autopsy 30% die of local disease only

Can Stereotactic body radiation therapy (SBRT) be delivered in the adjuvant setting?

- What volume(s) are covered?

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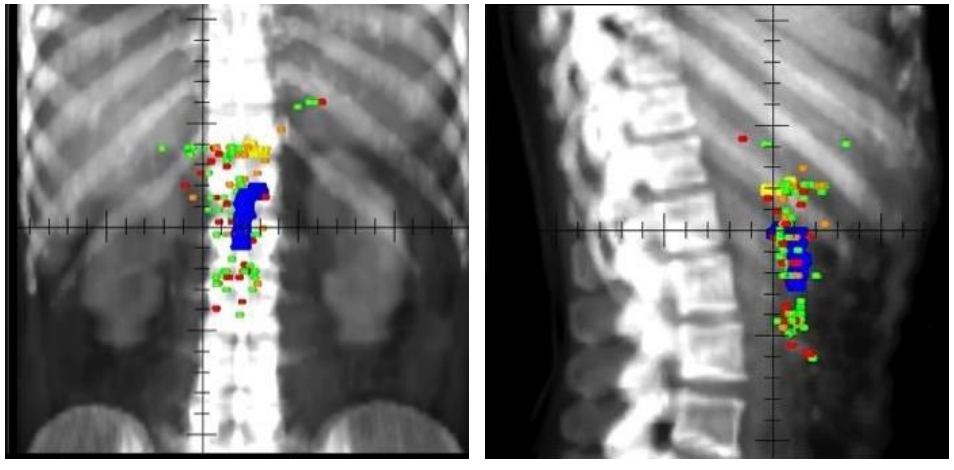
Prevent: Mapping area of Local Recurrences after surgery (+/- radiation)



Dholakia et al. 2013

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Contour the following additional OARs

Proximal structures: Region of the following OARs within 1 cm superior and inferior of the PTV boundary
Proximal jejunum
Proximal bowel
Proximal stomach

↓

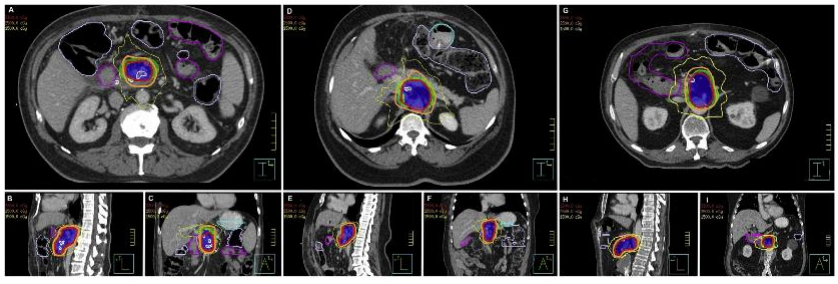
PTV80-Final and PTV90-Final Generation

Avoid the exterior of all proximal OARs by 3 mm

↓

Radiation treatment prescription

PTV80-Final: 6.6 Gy daily fractions for 5 days, 33 Gy total
PTV90-Final: 5.0 Gy daily fractions for 5 days, 25 Gy total



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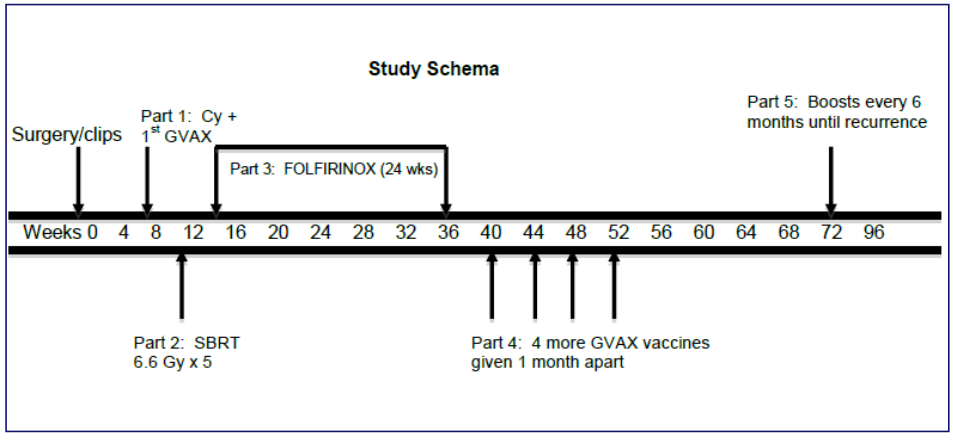
Pancreatic Vaccine, Low Dose Cytoxan, Fractionated SBRT, and FOLFIRINOX Chemotherapy in Patients with Resected Pancreatic Adenocarcinoma



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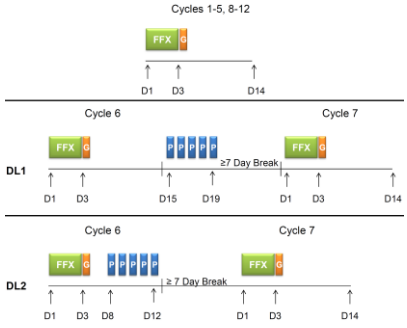
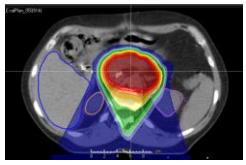
Phase I Study of Proton Therapy in Adjuvant Pancreatic Cancer (PROTON-PANC)





5G y X 5
fraction proton

DL = dose level, FFX = mFOLFIRINOX, G = pegfilgrastim on-body injector (optional), P = proton radiation (5 GyE).

ClinicalTrials.gov Identifier: NCT03885284

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Resectable Disease: Benefits of Neoadjuvant Therapy

Increases likelihood of R0 resection (particularly in borderline pts)

Avoids unnecessary surgery in those less likely to benefit

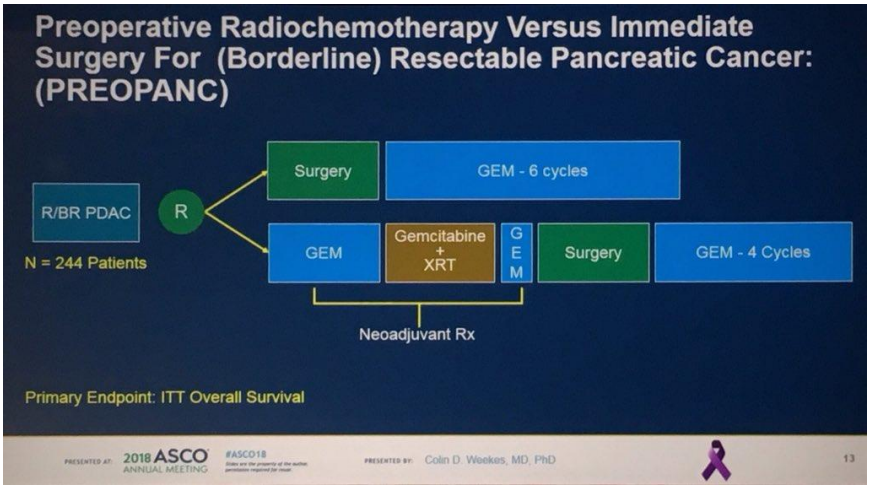
Minimizes delays in treatment/compliance

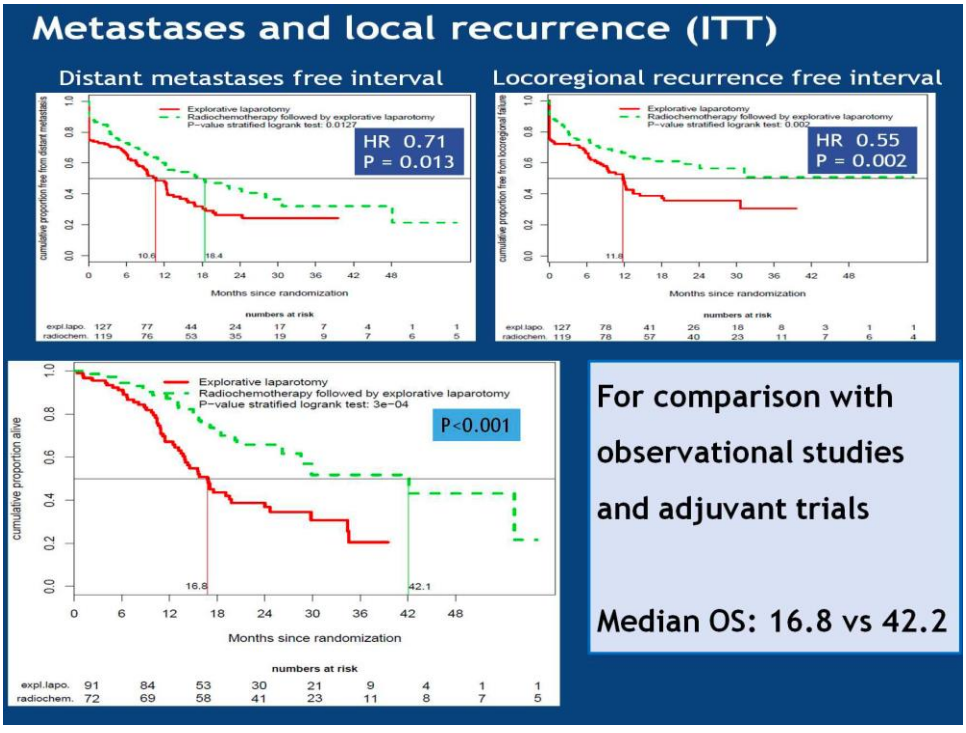
Smaller treatment fields/tumor delineation

Improves tumor related symptoms

Palta et al Oncology 2011

PREOPANC: Surgery vs. Neoadjuvant Therapy





Borderline Resectable Disease

Which Patients Should Be Taken to Surgery Following Neoadjuvant Therapy?

Most tumors do not "shrink" after neoadjuvant therapy

J Radiat Oncol (2013) 2:413–425
DOI 10.1007/s13566-013-0115-6

ORIGINAL RESEARCH

Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor–vessel relationships

Avani S. Dholakia · Amy Hacker-Prietz · Aaron T. Wild · Siva P. Raman · Laura D. Wood · Peng Huang · Daniel A. Laheru · Lei Zheng · Ana De Jesus-Acosta · Dung T. Le · Richard Schulick · Barish Edil · Susannah Ellsworth · Timothy M. Pawlik · Christine A. Iacobuzio-Donahue · Ralph H. Hruban · John L. Cameron · Elliot K. Fishman · Christopher L. Wolfgang · Joseph M. Herman

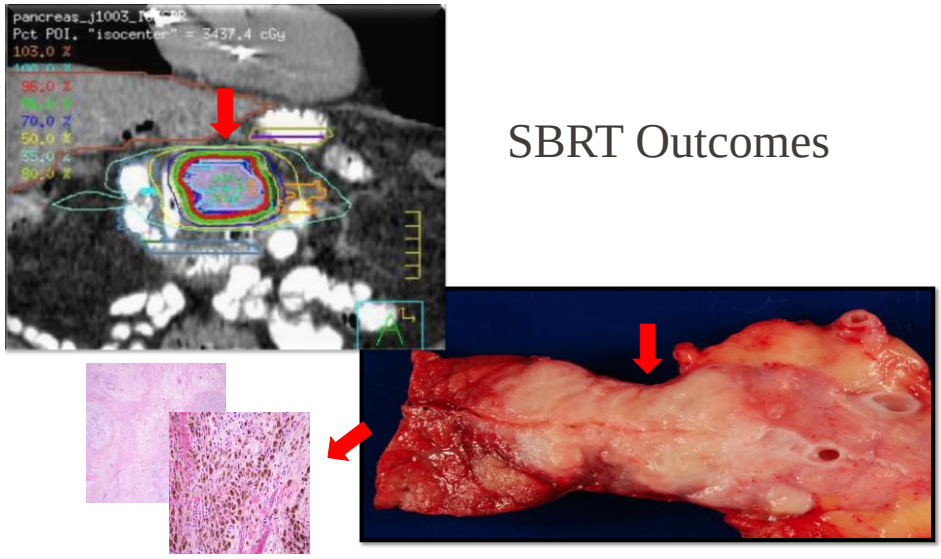
Neoadjuvant Therapy Improves Outcomes in BRPC

80-90% R0 resection rate

Study	n	Resectability (Criteria)	RT Dose (Gy)	Chemotherapy Regimen	Resection Rate (%)	R0 Resection Rate (%)	Median OS (mo)
Joensuu et al (2004)[87]	28	BR (MDACC)	50.4	Gem	75*	–	25.0
Pipas et al (2005)[43]	24	Res (17%) BR (29%) Unres (54%)	50.4	Doc + Gem → Gem	71	76	14.0
Talamonti et al (2006)[44]	20	Res (70%, Con) BR (30%, Con)	36	Gem	85	94	18.0 (Res 26.0)
Varadhachary et al (2008)[45]	79	Res (MDACC)	30	Gem + Cis → Gem	66	96	18.7 (Res 31.0 Unres 10.5, $P < .001$)
Small et al (2008)[46]	39	Res (41%) BR (23%) Unres (36%)	36	Gem	44	–	–
Evans et al (2008)[47]	86	Res (MDACC)	30	Gem	74	86‡	22.7 (Res 34.0 Unres 7.0, $P < .001$)
Lind et al (2008)[109]	17	BR (Con)	50.4	Cap + Ox	47	100	19.0
Katz et al (2008)[10]	84	BR (MDACC)	30-50.4	5-FU, Pac, Gem, Cap	38	97	21.0 (Res 40.0 Unres 15.0)
Maximous (2009)[110]	25	Unres	54	Gem	32	25	12.0
Landry (2010)[67]	10	BR (Con)	50.4	A) Gem	30	33	19.4 (Res 26.3)
	11	BR (Con)	50.4	B) 5-FU (induction Gem + Cis)	18	50	13.4 (Res 26.3)
Piperdi et al (2010)[111]	8	BR (MDACC)	50.4	5-FU or Gem	75	100	16.1† (No tx 14.0)
Turrini et al (2010)[48]	34	Res (Con)	45	Doc	50	100	15.5 (Res 32.0)
Stokes et al (2011)[112]	34	BR (MDACC)	50.4	Cap	46	75	Res 23.0 Unres 12.0
Leone et al (2012)[113]	39	BR (38.5%, Con) Unres (61.5%)	50.4	Gem + Ox → Gem	36	64 (82% BR, 18% Unres)	BR 27.8 Unres 12.3 $P = .045$
Pipas et al (2012)[49]	33	Res (12%) BR (70%, Con) Unres (18%)	54	Cetux → Gem + Cetux	76 (16% Res, 72% BR, 12% Unres)	92	17.3 (Res 24.3 Unres 10.0)
Habermehl et al (2012)[114]	198	Unres	Med 52.2	Gem	26	39	12.3 (R0 Res 22.1 Unres 11.9, $P = .003$)
Satoi et al (2012)[50]	34	Res BR (Con) Unres	50.4	S-1	88	93	–
Kim et al (2013)[65]	39	BR (NCCN)	30	Gem + Ox	62	84‡	18.4 (Res 25.4)
Takahashi et al (2013)[115]	80	BR (Con)	50	Gem	54	98	Res. 25.0 Unres 14.0
Van Buren et al (2013)[51]	59	Res (50%), BR (50%, Con)	30	Gem + Bev	73	88	16.8 (Res 19.7)
Eguchi et al (2014)[52]	21	Res	50.4	Gem + S-1	91	–	–

OS similar to that of resectable disease

Franke et al, Sem Oncol 2015



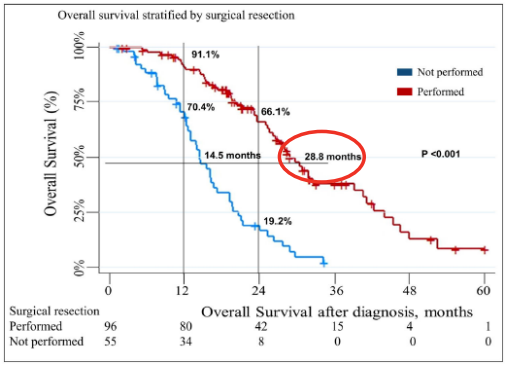
SBRT Outcomes

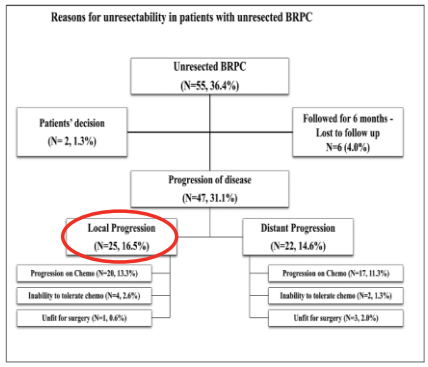
Does multi-agent chemotherapy combined with SBRT improve the likelihood that patients with LAPC or Borderline resectable PCA will undergo surgery?

Outcome of Patients with Borderline Resectable Pancreatic Cancer in the Contemporary Era of Neoadjuvant Chemotherapy

Ammar A. Javed[1,2], Michael J. Wright[1,2], Ayat Siddique[1,2], Alex B. Blair[1,2], Ding Ding[2,3], Richard A. Burkhart[1,2], Martin Makary[1,2], John L. Cameron[1,2], Amol Narang[2,4], Joseph Herman[2,4], Lei Zheng[2,3], Daniel Laheru[2,3], Matthew J. Weiss[1,2], Christopher Wolfgang[1,2], and **Jin He[1,2]**

[1]Department of Surgery, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Halsted 614, Baltimore, MD 21287, USA





- N=151: 63% were surgical, 73% after RT
- 51% received RT, RO resection 77%

J Gastrointest Surg. 2019 January

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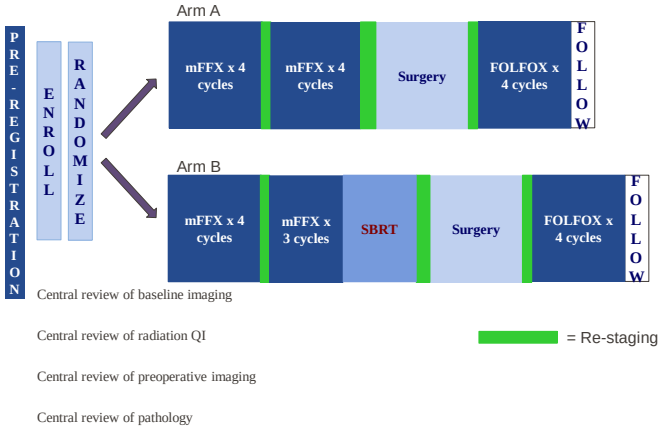
Alliance A021501: Preoperative Extended Chemotherapy Vs. Chemotherapy Plus Hypofractionated Radiation Therapy for BRPC of the Head of The Pancreas



- SBRT up to 40 Gy in 5 to tumor vessel interface (TVI)

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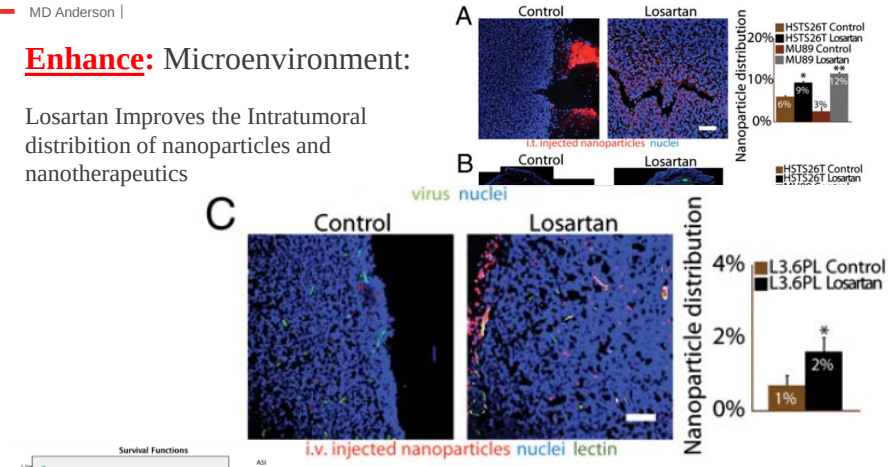
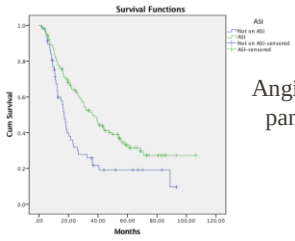
Enhance: Microenvironment:

Losartan Improves the Intratumoral distribition of nanoparticles and nanotherapeutics





Angiotensin inhibitor (ASI) use in resected pancreas cancer patients associated with improved survival

Liu et al. Clin Can Res 2017

MGH: Steele lab, Compliments Ted Hong

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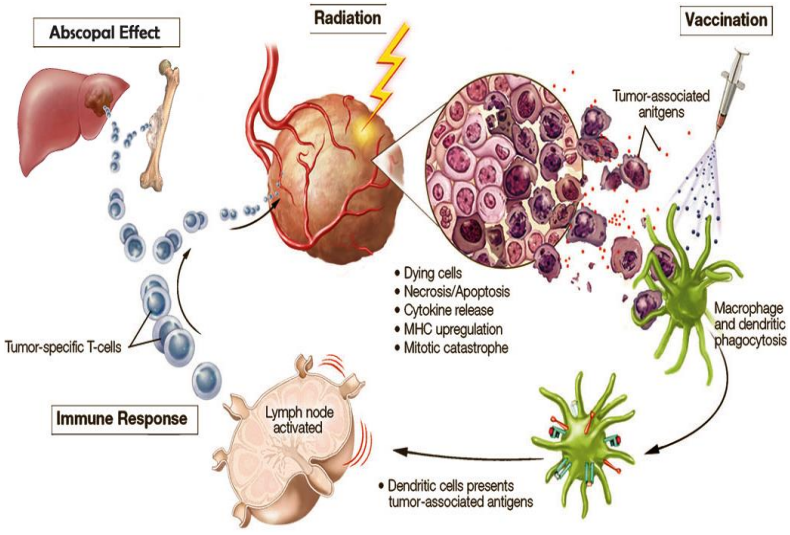
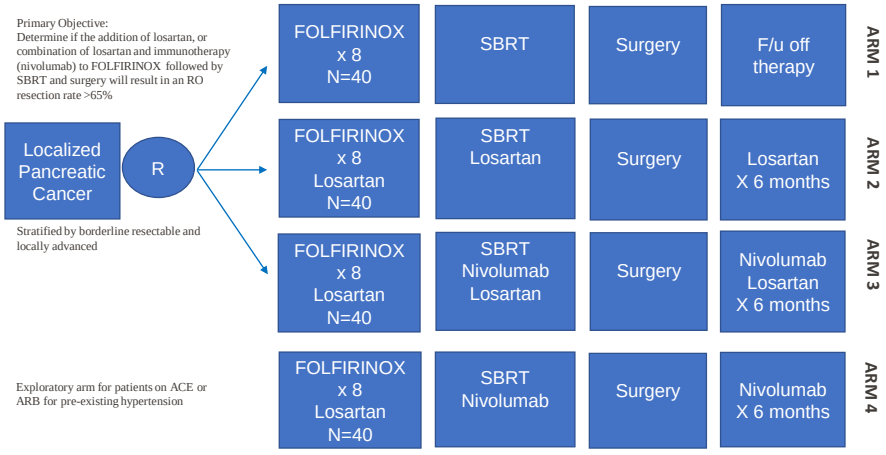
*Can we use RT to **enhance** immunotherapy?*



Kamrava M., Hodge JW., et al. Mol. BioSyst., 2009 - Adapted with Permission (Andrew Sharabi)

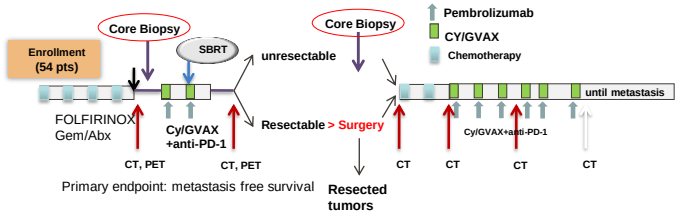
Enhance: SU2C trial

FFX + SBRT with or without Losartan, Nivolumab



Hong et al. Multicenter trial

Enhance: Vaccine/anti-PD-1 Antibody(Pembrolizumab) with Stereotactic Body Radiation following induction chemotherapy for locally Advanced PDAC

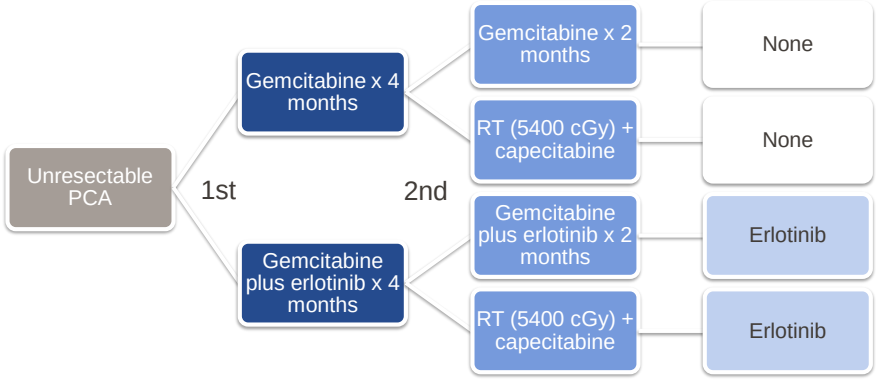


Lee, Jaffee Laheru, and Zheng: JHU

Locally Advanced or Unresectable Disease

Role of Radiation Therapy in Locally Advanced Disease (LAPC)?

GERCOR LAP-07 Trial



Hummel et al, JAMA 2016

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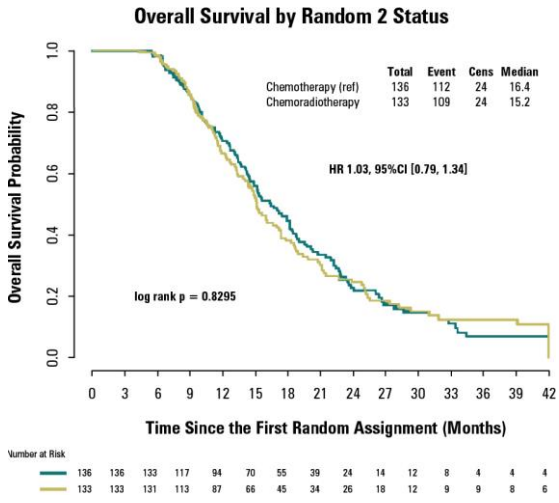
What Is The Role of Neoadjuvant Therapy in LAPC?

No survival benefit with RT

Only 60% included in 2nd randomization

Local control benefit with RT

With better chemotherapy, perhaps RT would have a larger impact



Hummel et al, JAMA 2016

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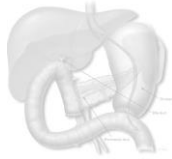
Surgical Exploration in LAPC



Radiographic evidence of tumor downstaging is not required for surgical evaluation

Under multidisciplinary review, consider the following:

1. ≥4 months of chemotherapy and no **distant metastases**
2. Good **performance status**/no limiting **comorbidities**
3. Stable or improved **CA 19-9, "technically resectable"**
4. Ideally, **<12 weeks after SBRT**

Katz MH, et al. *Cancer*. 2012;118(23):5749-5756
Dholakia AS, et al.. *J Radiat Oncol*. 2013 Dec;2(4):413-25

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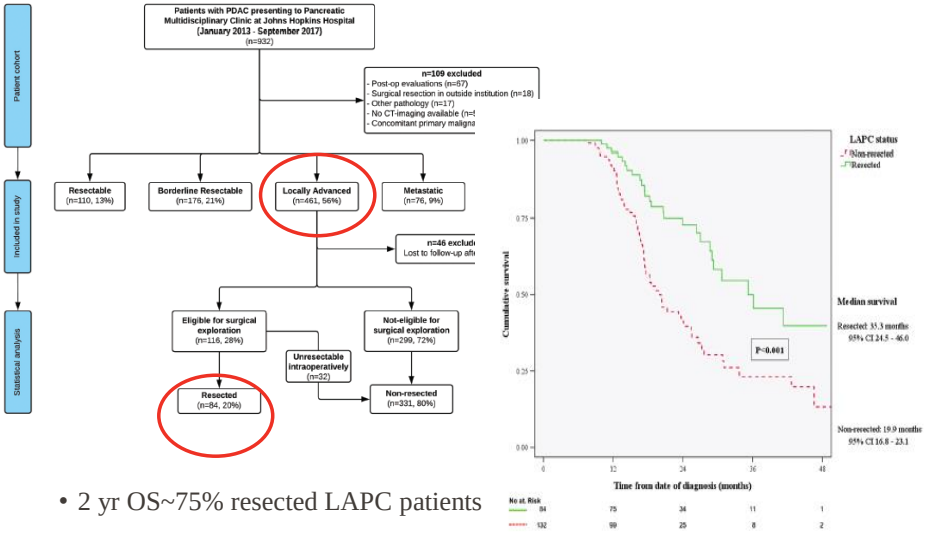
JHU Locally advanced PCA: Chemo + SBRT (+/- surgery)



- 2 yr OS~75% resected LAPC patients
- Med OS 35 months

Annals of Surgery 2018

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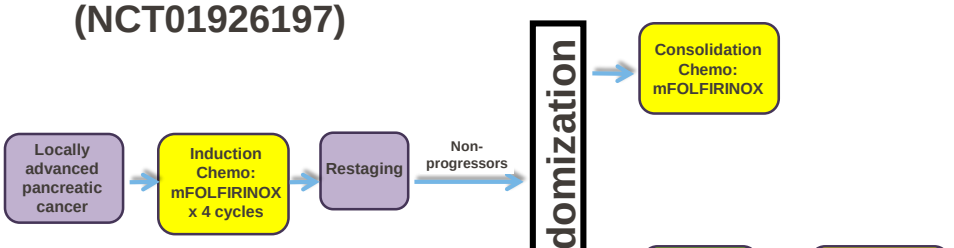
Phase III FOLFIRINOX (mFFX) +/- SBRT in Locally Advanced Pancreatic Cancer (NCT01926197)



- Primary Endpoint: Progression free survival at 1 year
- Patients may proceed to surgery if deemed resectable
- Chemo arm may proceed to SBRT if local only progression
- N=172
- Participating sites:
  - Stanford, PMH, Loyola, UTSW, MUSC
  - (pending) Duke, MDA

Houston area locations only

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Biological equivalent dose (BED) of ~100+ likely needed for adequate sterilization (durable) of the tumor and/or vessel margin

Optimal is unknown

3 fractions (42 Gy)

5 fractions (50 Gy)

15 Fractions (69 Gy)

25 Fractions (75 Gy)

Often depends on anatomy

Pancreas RT regimen comparisons (selection)

Conditions	Stereotactic body RT (SBRT) 5 Fx	Hypofractionation (Hypofx) 15 Fx	Standard (CRT) 25-30 Fx
GTV Goal (90Gy/BED)	50 Gy	67.5 Gy	75 Gy
Concurrent chemo	Rarely	Often	Almost always
Chemo concurrent	Capecitabine	Capecitabine/Gem	Capecitabine/Gem
Tumor ***Invades*** Bowel or Stomach*	Only if surgery guaranteed	Unknown risk of bleed/perforation	Assume less risk of bleed/perforation
Tumor ***abuts*** Bowel or stomach	If 90% of GTV can receive BED>90?	If GTV BED>90 not met with SBRT	If GTV BED>90 not met with hypofx
LN covered?	Proximal only	Yes	Yes
LRR recurrence risk*	++	++	+
Lymphopenia risk*	+	++	+++
Early/Late tox risk*	+/++	++/++	++/+
Patient time/cost*	+++ (Benefit)	++	+

**Limited data thus far, hypothesized*

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ABLATIVE RT RESULTS IN EXCELLENT LOCAL CONTROL AND SURVIVAL IN LOCALIZED PANCREATIC CANCER

M. Reyngold, E. O'Reilly, M Zinovoy, P. R. Romesser, A. J. Wu, C. Hajj, J.J. Cuaron, E.D. Yorke, A. M. Varghese, C. H. Crane

MSKCC

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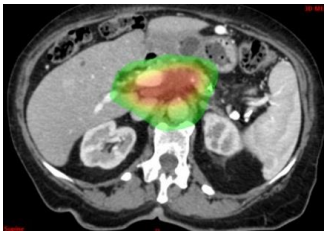
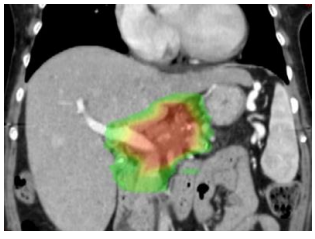
Anatomy-based dose prescription

Distance to luminal GI tract	Fractionation scheme	BED $_{a/b=10}$
< 1 cm	75Gy/25	97.5
> 1 cm	67.5Gy/15	97.88
> 2 cm	50Gy/5 (SBRT)	100





Adaptive re-planning in 10% based on daily CBCT

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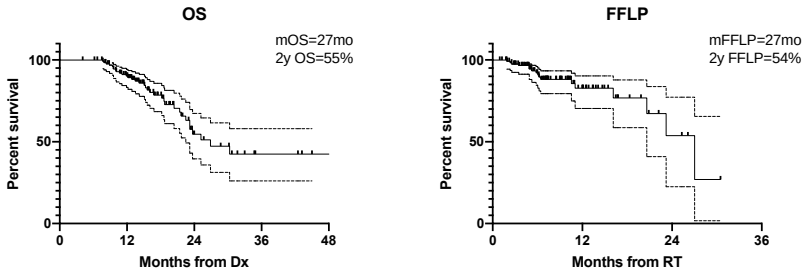
Definitive Cohort

N=136



Median follow up 16 mo

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Toxicity analysis

Toxicity Grade (CTCAE 4.03)	N (% of total)
UGI hemorrhage	
Grade 3	14 (8%)
Duodenal fistula	
Grade 1	1 (0.6 %)
Duodenal ulcer	
Grade 2	1 (0.6 %)
Bile duct stenosis	
Grade 3	5 (3%)
Vertebral body fractures	
Grade 2	4 (2%)

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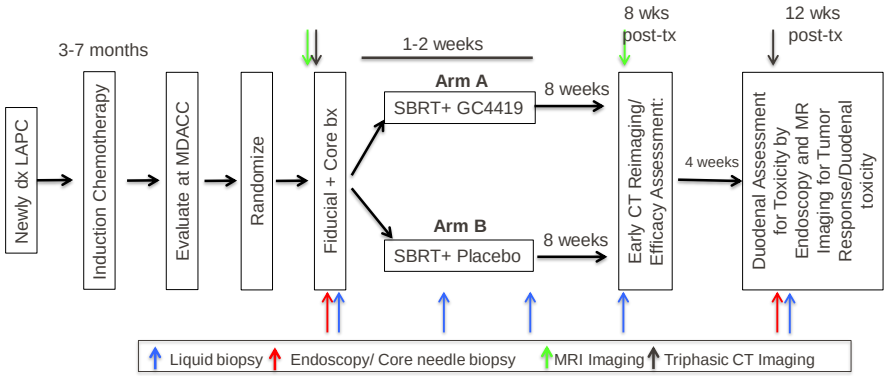
Protect: 2017-0606: An Adaptive Phase I/II Dose Escalation Trial of Stereotactic Body Radiation Therapy with a Radiomodulating Agent GC4419 (Galera) in Locally Advanced Pancreatic Cancer



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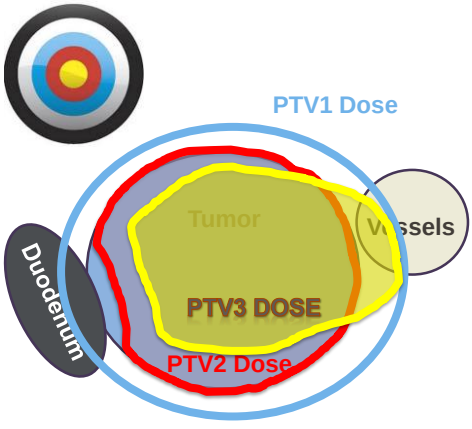
Three SBRT Dose Levels



Dose Level	Total Dose	Per Fraction	Tumor BED (a/b = 10)
1—10 Gy			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	40 Gy	8 Gy	72 Gy
PTV3	50 Gy	**10 Gy**	100 Gy
2—11 Gy			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	45 Gy	9Gy	86 Gy
PTV3	55 Gy	**11 Gy**	116 Gy
3—12Gy			
PTV1	33 Gy	6.6 Gy	55 Gy
PTV2	50 Gy	10 Gy	100 Gy
PTV3	60 Gy	**12 Gy**	132 Gy

- Plan to proceed to multicenter study 55 Gy in 5, BED 116 Gy

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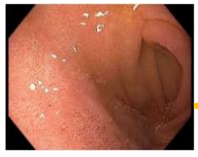
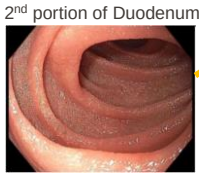
Example: Patient enrolled at MDACC

Grade 0 Tox @12 wks

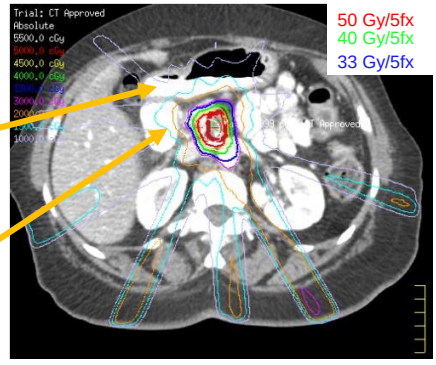
Duodenal bulb



2nd portion of Duodenum



SBRT Plan, Patient #1



SBRT plan of patient on protocol 2017-0606 who received 50Gy/5fx to the tumor in the pancreatic head. Endoscopy from Week 12 post-SBRT showing normal duodenum (Grade 0 toxicity). Post-tx biopsy done.

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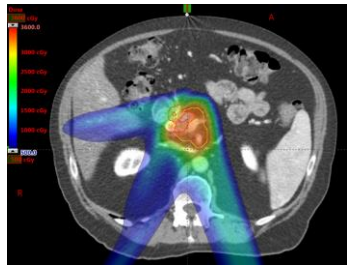
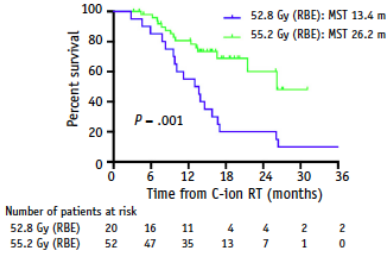
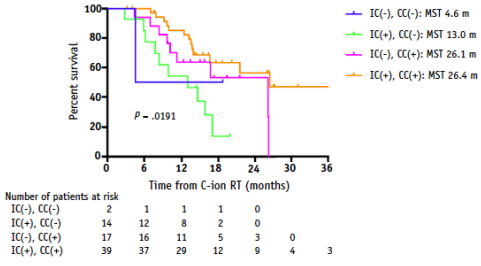
Radiobiology (RBE) and Avoid:
Carbon RT (Heavy Ions)







Survival improved with higher RT dose and induction (IC) and concurrent (CC) chemotherapy

2 yr OS~60%

Int J Radiation Oncol Biol Phys, Vol. 101, No. 5, pp. 1212–1221, 2018

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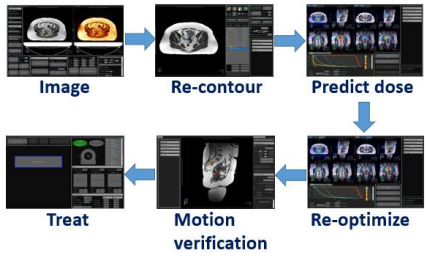
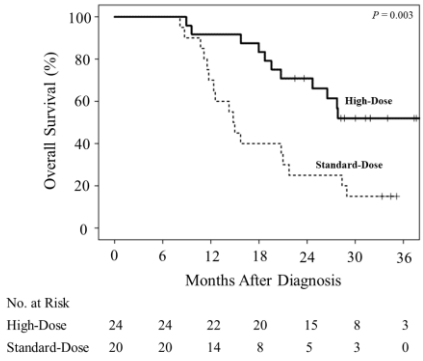
Adapt:
MRI guided RT (BED >90)





- Preliminary 70.8% 2-year survival BED>90 vs. 25% 2-year survival with BED <90 Gy (2), 15-25 fractions.

Henke L. Radiother Oncol. 2018 Mar;126(3):519-526.

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SMART – LAPC Consortium analysis

44 patients from 5 institutions w/ unresectable pancreatic ca; median follow-up 22.1 months

maxBED10 point dose

OS and LC from date of diagnosis

OS and LC stratified by maxBED10 compared with KM and with log-rank tests

S. Rudra, M. Roach, L. Porterlance, A. Bruynzeel, F. Lagerwaard, M. Bassetti,P. Parikh, and P. Lee, under 2nd revision

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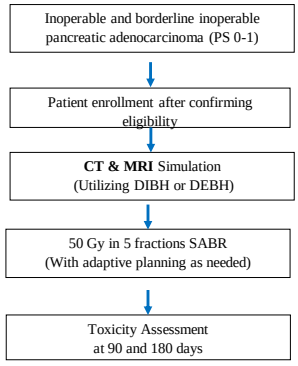
Phase II Study: Dose-Escalated Adaptive Stereotactic MRI-guided Ablative RadioTherapy (SMART) for locally advanced pancreatic cancer

MD: Co-PI: P. Parikh and P. Lee
Physics: O. Green, D. Low

Basic Eligibility
- Inoperable and borderline inoperable pancreatic adenocarcinoma
- PS 0-1
- No contraindications to MRI
- At least 12 weeks of systemic therapy prior to enrollment

Schema
- **50 Gy /5 fractions real-time adaptive SABR**



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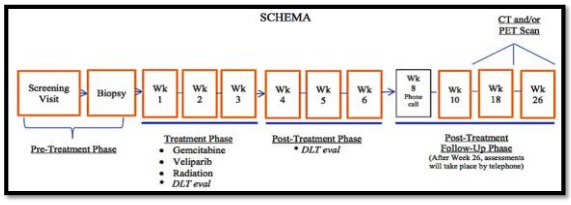
Sensitize: DDR: VelGemRad – NCT01908478

Phase I study: ABT-888 (VELiparib) in combination with GEMcitabine and IMRT for LAPC

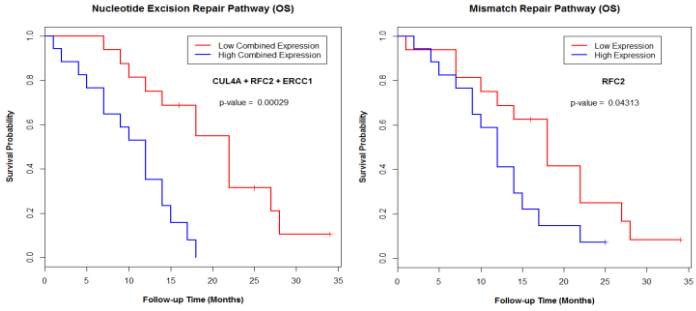
Study Treatment
- Gemcitabine: IV infusion of 1000 mg/m^2 on days 1, 8, 15 of the cycle
- IMRT: 36 Gy in 15 fractions (2.4 Gy/day, M-F)
- Veliparib: administered per dose escalation schema



- 1˚ Objective: to determine the MTD, safety and toxicity profile
- 2˚ Objectives:
  - Measure the clinical activity of the treatment (PFS, OS)
  - Evaluate tumor/blood pre/during/post treatment for DNA damage repair alterations, PAR levels and immune mediators

Ref: Tuli et al. EBioMedicine, https://doi.org/10.1016/j.ebiom.2018.12.060

DDR: VelGemRad – Transcriptome Analysis (OS)



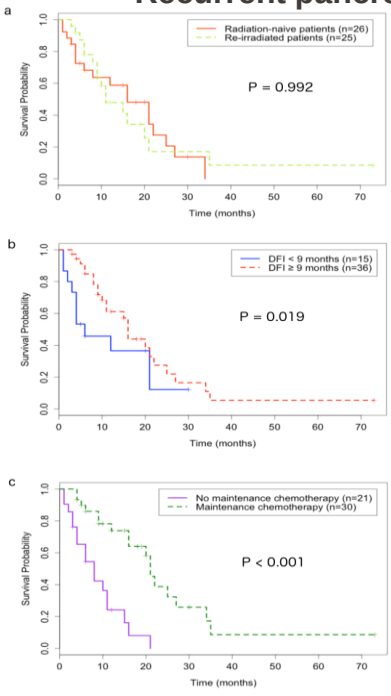
Median OS (biomarker + versus biomarker -)

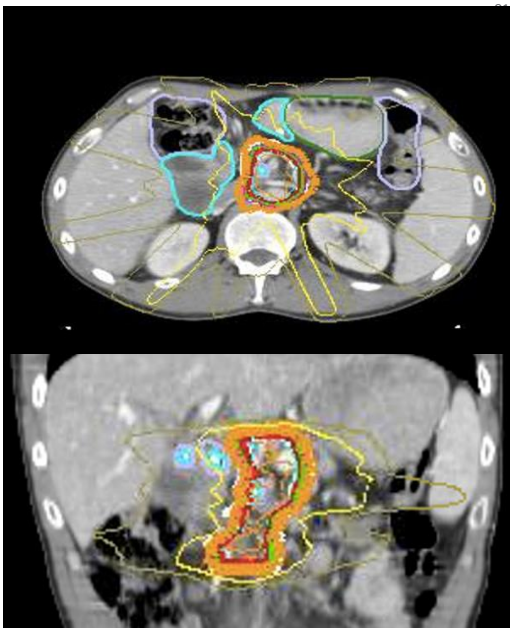
- NER - 22 vs. 12 mos, p<.001
- MMR - 18 vs. 12 mos, p<.05

Ref: Tuli et al. EBioMedicine, https://doi.org/10.1016/j.ebiom.2018.12.060

Recurrent disease and Re-irradiation

Recurrent pancreas cancer and Re-irradiation





Ryan et al. Ann Surg Oncol 25(1):280-289, 1/2018

Metastatic and Oligometastatic disease

Review

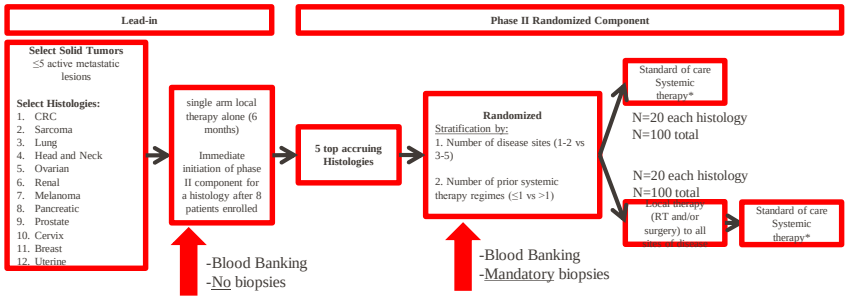
e29

Management of the Primary Tumor and Limited Metastases in Patients With Metastatic Pancreatic Cancer

Joseph M. Herman, MD, MSc[a]; John P. Hoffman, MD[b]; Sarah P. Thayer, MD, PhD[c]; and Robert A. Wolff, MD[d]

- J Natl Compr Canc Netw. 2015 May;13(5):e29-36.

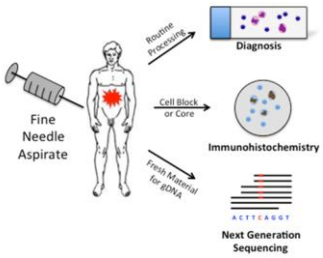
EXTernal beam radiation to Eliminate Nominal metastatic Disease (EXTEND): A randomized phase II basket trial to assess local control in the treatment of patients with oligometastatic disease

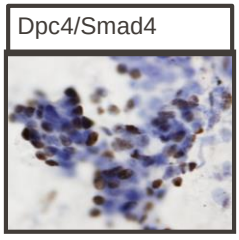


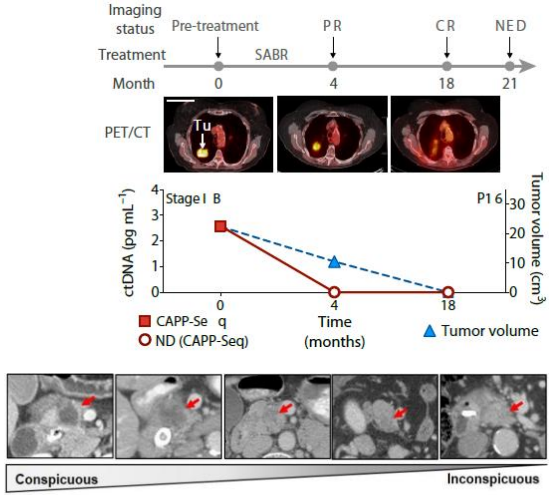
*Systemic therapy options include next line systemic therapy, maintenance therapy after an induction period, and continuing of the current line of systemic therapy. In the event that no reasonable standard of care systemic therapy options exist, patients can be treated with systemic therapy on a clinical trial or observed.

Chad Tang, PI MDA

Patient Selection: Which patients benefit from Radiation







Valero, Diehn, Koay, Iacobuzio-Donahue, et al.

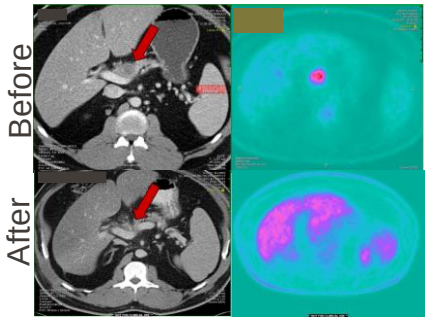
SBRT Tumor Response by PET

Mean SUVmax

- 5.14 → 3.13 (p<0.001)

Mean SUVpeak

- 4.01 → 2.40 (p<0.001)



Patient had a pCR

Dholakia et al.

Select (clinical factors):

OPEN

Factors Predicting Response, Perioperative Outcomes, and Survival Following Total Neoadjuvant Therapy for Borderline/Locally Advanced Pancreatic Cancer

Mark J. Truty, MD, MSc, FACS, Michael L. Kendrick, MD,* David. M. Nagorney, MD,* Rory L. Smoot, MD,* Sean P. Cleary, MD,* Rondell P. Graham, MD,† Ajit H. Goenka, MD,¶ Christopher L. Hallemeier, MD,§ Michel G. Haddock, MD,§ William S. Harmsen, MS,|| Amit Mahipal, MBBS,‡ Robert R. McWilliams, MD,‡ Thorvardur R. Halfdanarson, MD,‡ and Axel F. Grothey, MD‡*

N=194, 63% BLR

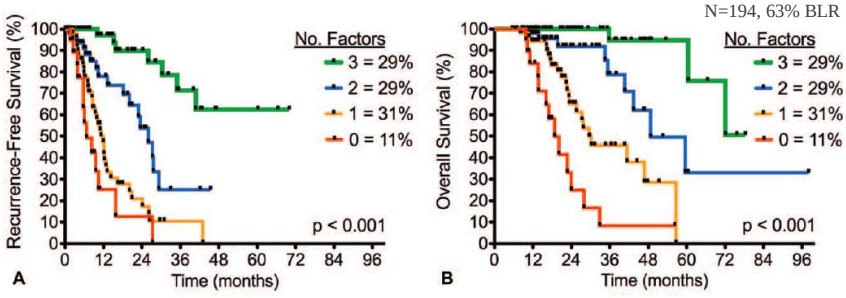


FIGURE 2. Kaplan-Meier survival curves stratified by number of predictive factors achieved. A, RFS and factor score. B, OS and factor score. All curves significant, $P < 0.001$.

Key factors OS: >6 mos chemo, Ca 19-9 response, pCR (0/1) Annals Surg Onc 2019

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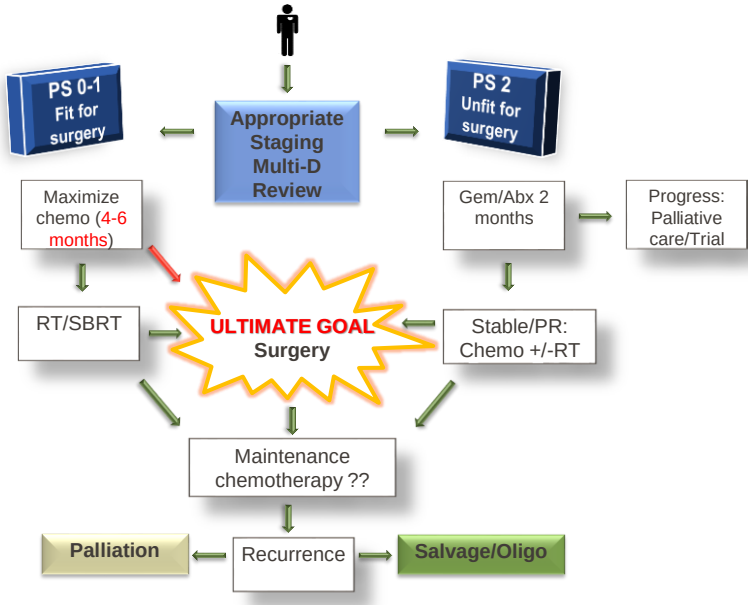
Localized pancreas cancer



Why ASTRO developed RT guidelines

ASTRO Pancreas Cancer Guidelines: Delivery of Therapy

KQ 1 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated RT with chemotherapy in select high-risk patients is conditionally recommended.	**Conditional**	**Low**	**92%***
Implementation Remark: High-risk clinical features would include positive lymph nodes and margins regardless of tumor location within the pancreas.			
2. Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry.	**Strong**	**Very low**	**100%***
3. For patients with resectable pancreatic cancer, neoadjuvant therapy is conditionally recommended.	**Conditional**	**Low**	**92%***

Neoadjuvant Therapy Resectable Pancreas: Conditional

Palta, PRO 2019 in press

Summary

RT technology

- New RT technologies allow for delivery of higher doses of RT with less toxicity
- RT dose based on biology, anatomy, expertise and technology (MR, particle therapy)
- BED >100 likely needed for ablation
- Multiple approaches to optimize dose and/or effectiveness
- Galera evaluating dose escalation (protection)
- Alliance SBRT BRPCA trial: Pending

SBRT Potentiation

- RT with PARP improves outcomes in select patients
- RT may enhance the tumor microenvironment
- RT causes lymphopenia, SBRT less
- Await results of SBRT with PD1 (JHU and SU2C)
- Optimal RT dose and timing unknown
- Need to simplify trials to enhance enrollment
- Need biomarkers to determine which patients need RT.

How do we maximize the therapeutic benefit(s) of radiation therapy in localized PCA?

- ***Goals: Achieve a pathologic complete response. R0 resection AND prevent local regional recurrence. Limit side effects, improve quality of life, and be cost-effective.***

1. Select regimen based on anatomy, biomarkers, performance status, and patient/family preference.

2. Avoid radiation dose to adjacent normal tissues or **protect** bowel/stomach.

3. Radiobiology: Heavy Ions (protons/Carbon) give better radiobiological equivalent (RBE) dose to tumor with sharp fall-off of RT dose.

4. **Adapt:** use (CT on rails, PET, or MR) to better visualize tumor and nl tissues.

5. **Sensitize:** the effects of RT with Parp inhibitors or other drugs/agents.

6. **Enhance:** the tumor microenvironment for immunotherapy.

7. **Prevent:** recurrence after surgery or local progression after chemo/RT.

Ongoing clinical trials

Study	Phase	Location	Description	Stage	Primary Outcome	Total (Gy)	No. Fractions	Gy/Fx	BED_3	BED_{10}
NCT02873598	1	Denver, CO	Dose escalation of SBRT+FOLFIRINOX or gem/abraxane	LAPC	MTD, DLTs	27	3	9	108	51.3
	—	—	—	—	—	30	—	10	130	60
	—	—	—	—	—	33	—	11	154	69.3
NCT02643498	1	NYC, NY	SBRT after induction chemo	LAPC	MTD, DLTs	27	3	9	108	51.3
	—	—	—	—	—	30	—	10	130	60
	—	—	—	—	—	33	—	3	154	69.3
	—	—	—	—	—	42	6	7	140.0	71.4
	—	—	—	—	—	54	12	4.8	135.0	78.3
						67.5	15	4.5	168.8	97.9
NCT03158779	2	Milan, Italy	SBRT+FOLFIRINOX or gem/abraxane	LAPC	MTD, DLTs	54	6	9	216	102.6
NCT02454140	1	San Diego, CA	Dose escalation of SBRT	LAPC	MTD	40	5	8	146.6	72
	—	—	—	—	—	45	—	9	180	85.5
	—	—	—	—	—	50	—	10	216.6	100
	—	—	—	—	—	55	—	11	256.6	115.5
	—	—	—	—	—	60	—	12	300	132
NCT01926197	3	Palo Alto, CA	FOLFIRINOX ± SBRT	LAPC	PFS	NR	NR	NR	—	—
NCT02128100	2	Louisville, KY	FOLFIRINOX+SBRT	LAPC	Toxicity up to 24 mo posttreatment	32	5	6.5	101.3	52.8
NCT02734680	NR	Beijing, China	IORT followed by CCRT or SBRT, then S-1*	LAPC	OS	45	15	3	90	58.5
NCT02648282	2	Baltimore, MD	CY, Pembrolizumab, GVAX, followed by SBRT	LAPC	DMFS	33	5	6.6	105.6	54.8
NCT02461836	2	Zhejiang, China	Gem+SBRT after radical T3 or N1 resection	Resectable	DFS	25	5	5	66.7	37.5
NCT02347618	2	Rochester, NY	Short course of preoperative SBRT	Resectable	Grade ≥2 toxicity up to 24 mo	NR	NR	NR	—	—
NCT02308722	1	Glasgow, UK	Preoperative SBRT dose escalation†	BRPC	MTD	30	5	6	80	45
	—	—	—	—	—	32.5	5	6.5	102.9	53.4
	—	—	—	—	—	35	5	7	116.6	59.5
NCT02704156	2	Shanghai, China	5 fraction SBRT	LAPC	MST	45‡	5	9	180	85.5
NCT01342354	1	Chicago, IL	Dose escalation of SBRT	Unresectable, LRPC	MTD	NR	NR	NR	—	—
NCT01872377	1	Ottawa, Canada	Dose escalation SBRT boost	LAPC	Grade 3–4 GI toxicity up to 36 mo	18	3	6	54	28.8

Ongoing clinical trials: part 2

Study	Phase	Location	Description	Stage	Primary Outcome	(Gy)	No. Fractions	Gy/Fx	BED_3	BED_{10}
NCT02416609	NR	Modena, Italy	LDR+GemOx and SBRT	LAPC	PFS	NR	NR	NR	—	—
NCT02704143	2	Shanghai, China	SBRT with S1	LAPC	MST	NR	NR	NR	—	—
NCT02868632	1	NYC, NY	SBRT with durvalumab ± tremelimumab	Unresectable	OS	30	5	6	90	48
NCT02208024	1	Cincinnati, OH	5 fraction SBRT	Resectable	Acute grade ≥ 3 toxicity	33	4	6.6	105.6	54.8
NCT01918644	1	Madison, WI	Preoperative cape+SBRT	Resectable	DLT	NR	NR	NR	—	—
NCT01959672	2	Omaha, NE	Neoadjuvant chemo ± oregovomab with concurrent SBRT+nelfinavir	Resectable, BRPC, LAPC	Rate of disease progression	NR	5	NR	—	—
NCT01781728	2	Baltimore, MD	Palliation with SBRT	LRPC, residual disease	Late grade >2 toxicity	33	5	6.6	105.6	54.8
	—	—	—	—	—	25	5	5	66.7	37.5
NCT03099265	2	New Haven, CT	Neoadjuvant mFOLFIRINOX+SBRT	BRPC	R0 resection rate	33	5	6.6	105.6	54.8
NCT03073785	2	Omaha, NE	SBRT+5-FU or cape ± zoledronic acid	LAPC	LC at 4 mo	NR	5	NR	—	—
NCT02311361	1	Bethesda, MD	Dose escalation of SBRT with durvalumab and/or tremelimumab	Unresectable	Adverse event frequency	8	1	8	29.3	14.4
	—	—	—	—	—	25	5	5	66.7	37.5
NCT02241551	2	Pittsburgh, PA	Gem/nab-paclitaxel or FOLIRINOX+SBRT	BRPC	Safety of Gem/abraxane, R0 resection rate, pCR	NR	NR	NR	—	—
NCT02950025	2	St. Louis, MO	Online adaptive vs. nonadaptive SBRT	Unresectable, oligometastatic	Grade ≥3 toxicity	50	5	10	216.6	100
NCT02870648	1	Indianapolis, IN	Respiratory-gated SBRT	Resectable, BRPC, LAPC	Acute grade ≥ 3 toxicity	33	5	6.6	105.6	54.8
	—	—	—	—	—	30	5	5	90	48
NCT02723331	2	Denver, CO	Perioperative Gem/abraxane followed by SBRT	Resectable, BRPC	R0 resection rate	NR	NR	NR	—	—
NCT02153450	1	Cleveland, OH	SBRT+metformin	BRPC, LAPC	DLT	NR	NR	NR	—	—
NCT01357525	2	Pittsburgh, PA	SBRT following R1 or close margin resection	Resectable	LPFS	36	3	12	180	79.2
NCT03245541	1 and 2	Los Angeles, CA	Durvalumab+SBRT	LAPC, BRPC	DLT, PFS	30	5	6.6	105.6	54.8

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Things to know and ask. A patients perspective.

I am fighting this disease for myself and others. My goal is to help and guide other PC patients through this difficult journey!

- Get a second opinion (PANCAN)
- There is always hope
- Find oncologists who have treated a substantial # of patients with PC
- Your institution(s) need a team and tumor board that reviews your case often
- Read read read up on the disease
- Be able to access your medical records
- Know where your tumor is located, stage
- What are the side effects and how you can prepare to manage them?
- Remember this is your JOURNEY and YOU are your best ADVOCATE!
- Look at Trials
- Remember everyone's PC is unique
- Exercise, know what and how to eat
- Pancreas enzymes, pain management

Thank you!

- JHU: Chris Wolfgang, Liz Jaffee, Dan Laheru, Valerie Lee, Jin He, Lei Zheng, Linda Chen, and Amol Narang (rest of MDC team)
- Ted Hong, MGH
- George Miller, NYU
- Parag Parikh, Wash U.
- MSKCC: Linda Chen, Chris Crane
- Percy Lee: MDACC

SU2C Neoadjuvant Study Team

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Grant Co-PI- Alec Kimmelman (NYU)

Study PI- Ted Hong (MGH)

Translational lead (Organoids)- Rick Burkhart (JHU)

Translational lead (liquid biopsies) – David Ting (MGH)

Project Manager- Leilana Ly (MGH)

Participating Institutions

- Massachusetts General Hospital
  - Dana-Farber Cancer Institute
  - Beth Israel-Deaconess
- New York University
- Johns Hopkins University
- MD Anderson
- University of Colorado

Thank you for your participation.
If you have questions, please contact

Patient Central at
877-2-PANCAN or e-mail patientcentral@pancan.org.

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