

Maximizing Tumor control and Limiting Toxicity
With SBRT for Pancreas Cancer

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1

Objectives

- Current role of radiation in Pancreas Cancer
- Significance of local control and control of distant metastasis
- SBRT for pancreas cancer
- Clinical scenarios for exploring future role



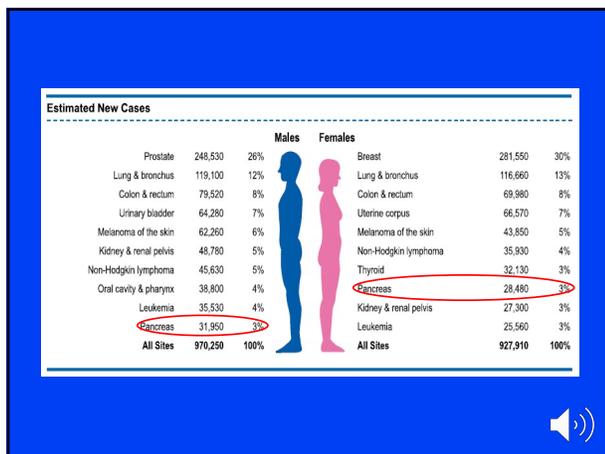
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Fundamental Principles

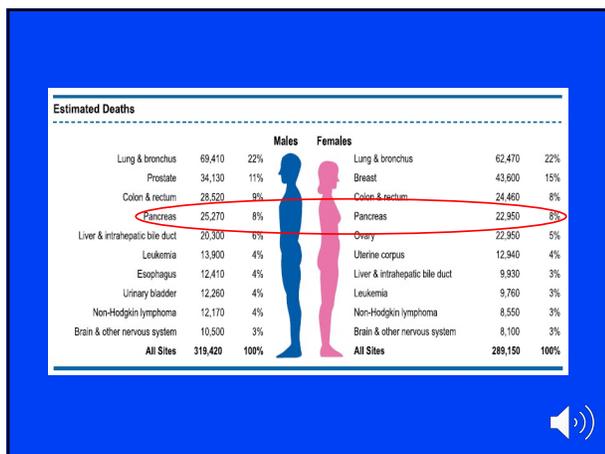
- Surgery is the primary curative treatment for Cancer
- Systemic therapy is essential component in the multimodality management of cancer
- Radiation therapy is more about protecting normal tissue than treating cancer



3



4



5

Perspective

Table 1. Median survival of patients in different stages of pancreatic cancer.

Stage	Incidence	Median survival
Localized/resectable	10%	15-19 months
Locally advanced	30%	6-10 month
Metastatic	60%	3-6 months

6

Clinical Scenarios Where SBRT can play a role in Pancreas Cancer

- Resectable Pancreas cancer
 - Neoadjuvant SBRT
 - Adjuvant SBRT
- Borderline resectable Pancreas Cancer
- Locally advanced
- Metastatic Pancreas Cancer
 - Oligometastatic Pancreas Cancer
- Local recurrence



7

Local Disease Staging Intergroup radiographic criteria

	Potentially Resectable	BORDERLINE RESECTABLE	Locally Advanced
SMV-PV	T-V-I < 180°	T-V-I ≥ 180° and / or reconstructable occlusion	Unreconstructable Occlusion
SMA	No T-V-I	T-V-I < 180°	T-V-I ≥ 180°
CHA	No T-V-I	Reconstructable short-segment T-V-I of any degree	Unreconstructable
Celiac Trunk	No T-V-I	T-V-I < 180°	T-V-I ≥ 180

T-V-I: tumor-vessel interface



8

Resectability Status	Arterial	Venous
Resectable	<ul style="list-style-type: none"> • No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). 	<ul style="list-style-type: none"> • No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or SMA contact without vein contour irregularity.
Borderline Resectable^b	<p>Pancreatic head/uncinate process:</p> <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <p>Pancreatic body/tail:</p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Aggleby procedure (some panel members prefer these criteria to be in the locally advanced category). 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of >180° contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced^{b,c}	<p>Head/uncinate process:</p> <ul style="list-style-type: none"> • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° <p>Pancreatic body/tail:</p> <ul style="list-style-type: none"> • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement 	<ul style="list-style-type: none"> • Unreconstructable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)



9

RESECTABILITY

- No distant metastases
- No arterial or venous involvement
- Attachment to other organs (eg, spleen)
- Venous involvement (SMV or portal) less than 180 degrees, as long as there is suitable vessel proximal and distal to the areas of involvement for reconstruction
- Gastroduodenal artery encasement up to the common hepatic artery with other short segment encasement or abutment of the hepatic artery, but without extension to celiac trunk
- Tumor abutment of the SMA less than one-half the circumference of the vessel wall.
- Greater than 180 degree encasement or occlusion/thrombus of SMA, unreconstructable SMV or SMV-portal vein confluence occlusion
- Direct involvement of the inferior vena cava, aorta, celiac trunk or hepatic artery, as defined by absence of a fat plane between low density tumor and these structures on CT or EUS.
- Metastases to lymph nodes beyond the peripancreatic tissues
- Distant metastases

10

Locally Advanced Pancreas Cancer

11

Classic Trials: RT vs. ChemoRT and Chemo vs. ChemoRT

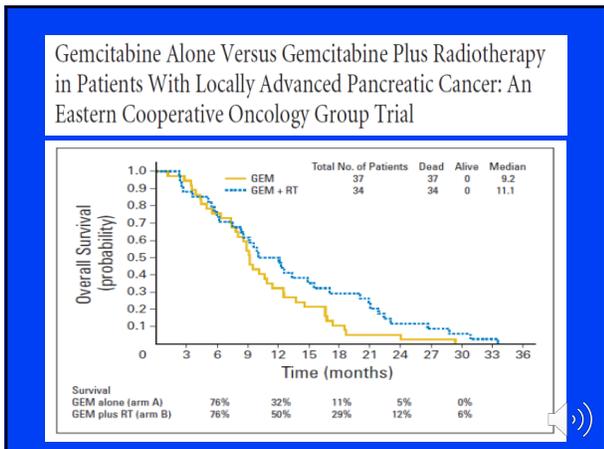
Study and Treatment	No. of Patients	Median PFS (months)	Median OS (months)	1-Year Survival (%)
FU-based CRT				
Moertel et al ⁵ ; phase III				
RT 60 Gy	25	2.9	5.3	10
RT 40 Gy/FU	83	5.3	8.4*	35
RT 60 Gy/FU	86	7.75	11.4*	46
Klaassen et al⁶; phase III				
FU	44	4.4	8.2	32
RT 40 Gy/FU	47	4.2	8.3	26
GITSG et al⁷; phase III				
SMF	21	—	7.4	19
RT 54 Gy/FU and SMF	22	—	9.7*	41
Cohen et al¹⁰; phase III				
RT 59.4 Gy	49	5	7.1	—
RT 59.4 Gy/FU + mitomycin	55	5.1	8.4	—

12

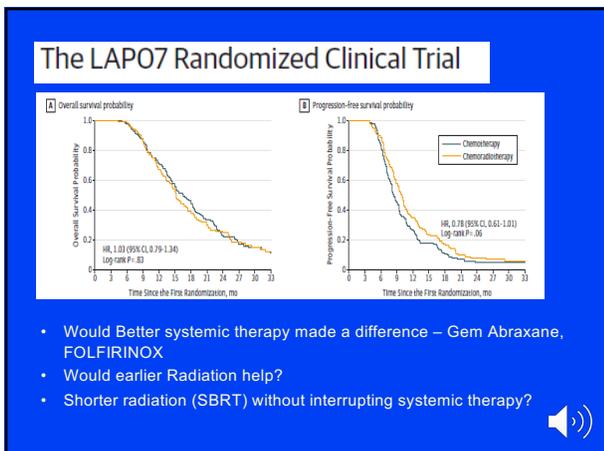
Contemporary Chemo-radiation Trials

Trial	Treatment	No of Pts	Med OS
RTOG 9812	50.4Gy+Taxol	122	11.3m
RTOG 0020	50.4Gy+Taxol/Gem	154	11.7m
RTOG0411	50.4Gy+Xeloda/Avastin	94	11.9m
FFCD-SSRO	60Gy+5FU/Cisplat	59	8.6m
ECOG 4201	50.4Gy+Gem	34	11.0m

13



14



15

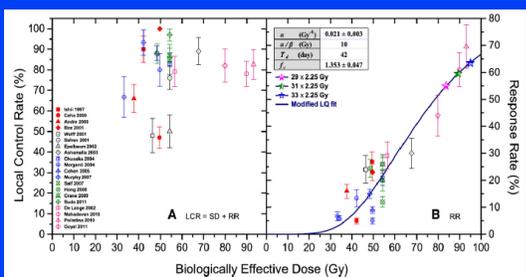
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RTOG 9812	50.4Gy+Taxol	122	11.3m
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RTOG0411	50.4Gy+Xeloda/Avastin	94	11.9m
FFCD-SSRO	60Gy+5FU/Cisplat	59	8.6m
ECOG 4201	50.4Gy+Gem	34	11.0m

16

Radiation dose responses for chemoradiation therapy of pancreatic cancer: An analysis of compiled clinical data using biophysical models

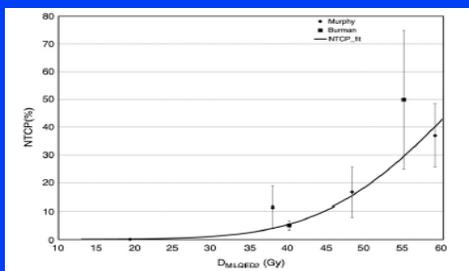
Ion C. Moraru PhD, An Tai PhD, Beth Erickson MD, X. Allen Li PhD*



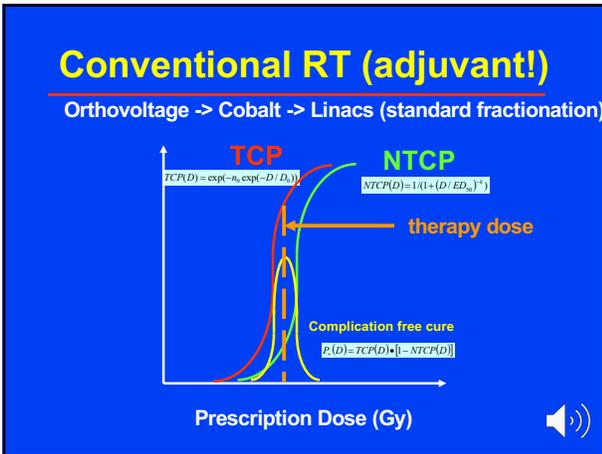
17

Consolidating duodenal and small bowel toxicity data via isoeffective dose calculations based on compiled clinical data

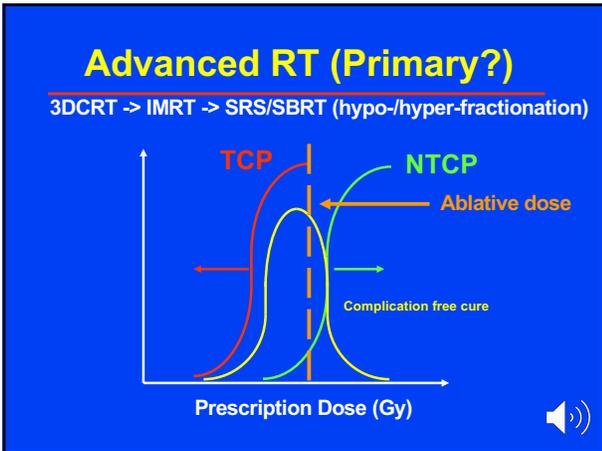
Phillip Prior PhD, An Tai PhD, Beth Erickson MD, X. Allen Li PhD*



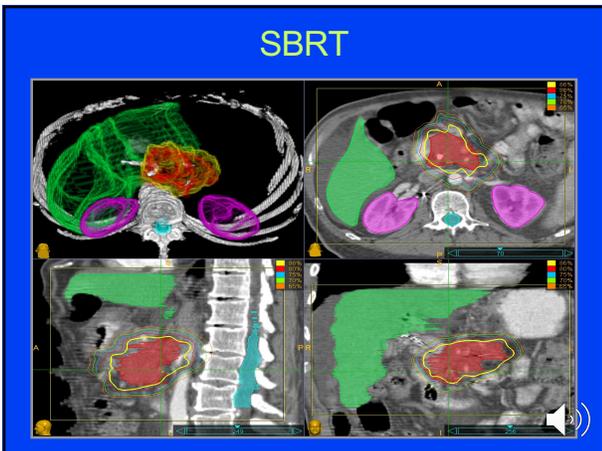
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19



20



21

SBRT

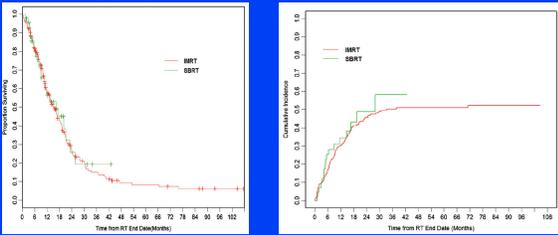
- Stanford Phase I
- Stanford EBRT+ Boost
- Stanford Gem SBRT
- Danish Phase II
- UPMC
- Sinai, Baltimore
- BIDMC Upfront SBRT
- BIDMC Gem SBRT
- Tampa
- Hopkins/Stanford/Memorial



22

Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer

Joseph J. Park^a, Carla Haji^b, Marsha Revngold^a, Weijl Shi^b, Zhiqiang Zhang^b, John J. Cuaron^a



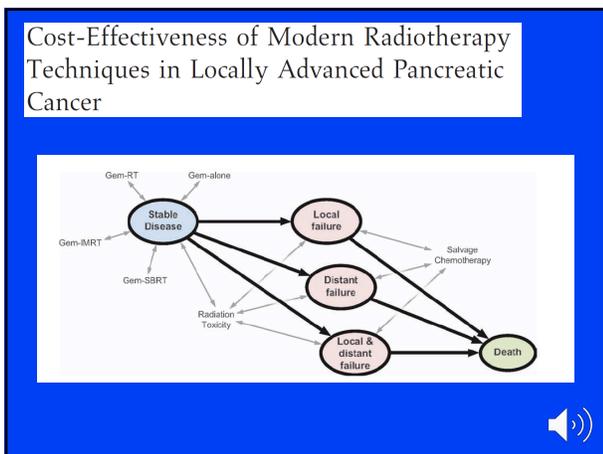

23

Acute toxicity	IMRT (n = 227)	SBRT (n = 44)	p Value
Grade 2+ GI			0.008
No	171 (76%)	41 (93%)	
Yes	55 (24%)	3 (7%)	
Grade 3+ GI			1.00
No	221 (98%)	44 (100%)	
Yes	5 (2%)	0 (0%)	
Grade 2+ fatigue			<0.0001
No	130 (58%)	41 (93%)	
Yes	96 (42%)	3 (7%)	
Grade 3+ hematologic			0.001
No	167 (74%)	42 (95%)	
Yes	59 (26%)	2 (5%)	

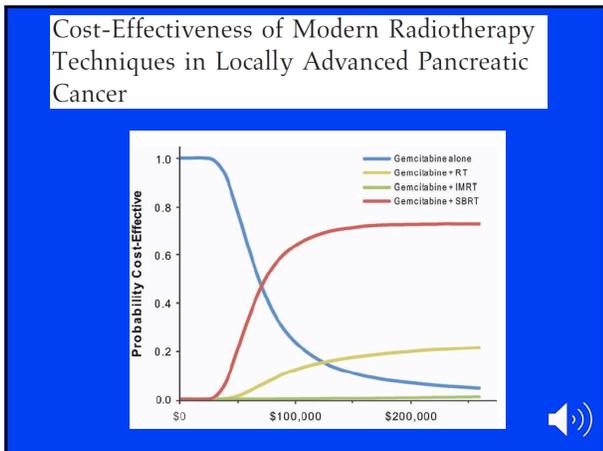
IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy.



24



25



26

Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Edward P. Balaban, Pamela B. Mangu, Alok A. Khorana, Manish A. Shah, Somnath Mukherjee,

Recommendation 3.1: If there is local disease progression after induction chemotherapy, but without evidence of systemic spread, then CRT or **SBRT** may be offered to patients who meet the following criteria: First-line chemotherapy treatment is completed or terminated because of progression or toxicity; ECOG PS \leq 2; a comorbidity profile that is adequate, including adequate hepatic and renal function and hematologic status; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.2: CRT or **SBRT** may be offered to patients who have responded to an initial 6 months of chemotherapy or have stable disease but have developed unacceptable chemotherapy-related toxicities or show a decline in performance status, as a consequence of chemotherapy toxicity (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.3: If there is response or stable disease after 6 months of induction chemotherapy, CRT or **SBRT** may be offered as an alternative to continuing chemotherapy alone for any patient with LAPC (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

27

ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Table 2 Recommendations for indications for conventionally fractionated RT or SBRT

KQ 1 recommendations	Strength of recommendation	Quality of evidence	Consensus
For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended.	Conditional	Low	77%*
For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended.	Conditional	Low	85%*



28

For patients with borderline resectable pancreatic cancer selected for SBRT, 3000-3300 cGy in 600-660 cGy fractions with a consideration for a simultaneous integrated boost of up to 4000 cGy to the tumor vessel interface is conditionally recommended.	Conditional	Moderate	100% [†]
For patients with locally advanced pancreatic cancer selected for SBRT, 3300-4000 cGy in 660-800 cGy fractions is recommended.	Strong	Moderate	100% [†]
For patients with borderline resectable pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.	Strong	High	92% [†]
Implementation Remark: SBRT does not routinely treat elective nodes.			
For patients with locally advanced pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.	Strong	High	100% [†]



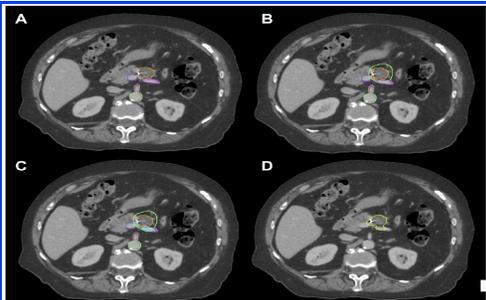
29

Description	Planning System Name	Constraints
Modified PTV	mPTV	V25 > 95% (range 25-40 Gy)
PTV	PTV	V20 > 95%
OAR		Constraints
Duodenum	Duodenum	V15 < 9cc V20 < 3cc V33 < 1cc
Small Bowel	Bowel	V15 < 9cc V20 < 3cc V33 < 1cc
Stomach	Stomach	V15 < 9cc V20 < 3cc V33 < 1cc
Liver	Liver	V12 < 50%
Combined Kidneys	Kidneys	V12 < 75%
Spinal Cord	Spinal Cord	V20 < 1cc
Spleen	Spleen	No constraint



30

Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT)



31

Table 2 Suggested dose constraints for pancreas SBRT

Organ	Standardized name	Parameter	Constraint		
			Constraint	Per protocol, Gy	Minor variation, Gy
Duodenum	Duodenum	Dmax (0.5 cm ³)	<33	≤35	>35
		V30	<5 ^a	5-10 ^a	>10 ^a
Stomach	Stomach	Dmax (0.5 cm ³)	<33	≤35	>35
		V30	<5 ^a	5-10 ^a	>10 ^a
Small bowel	SmallBowel	Dmax (0.5 cm ³)	<33	≤35	>35
		V30	<5 ^a	5-10 ^a	>10 ^a
Large bowel	LargeBowel	Dmax (0.5 cm ³)	≤35 Gy	35-38 Gy	>38
Duodenum PRV ¹	Duodenum_PRV	Dmax (0.5 cm ³)	<38 Gy	38-40 Gy	>40
Small bowel PRV ¹	SmallBowel_PRV	Dmax (0.5 cm ³)	<38 Gy	38-40 Gy	>40
Large bowel PRV ¹	LargeBowel_PRV	Dmax (0.5 cm ³)	<38 Gy	38-40 Gy	>40
Stomach PRV ¹	Stomach_PRV	Dmax (0.5 cm ³)	<38 Gy	38-40 Gy	>40
Spinal cord PRV	SpinalCord_05	Dmax (0.5 cm ³)	<20 Gy	≤25 Gy	>25
Combined kidneys	Kidneys_Comb	V12 ²	<25 ²	25-30 ³	>30 ³
		V10 ⁴	<10 ⁴	10-25 ⁵	>25 ⁵
Single kidney	Kidney_L Kidney_R	V12 ²	<40 ¹	≤50 ³	>50 ³
		V10 ⁴	<10 ⁴	10-25 ⁵	>25 ⁵
Liver	Liver	V12 ²	<40 ¹	≤50 ³	>50 ³

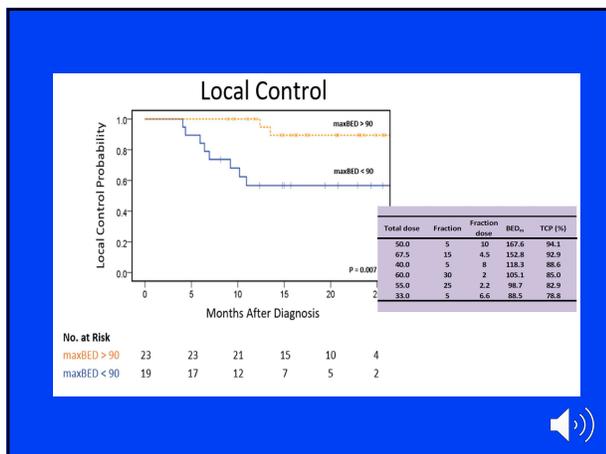
Abbreviations: Dmax = maximum dose; PRV = planning organ-at-risk volume; SBRT = stereotactic body radiation therapy.

32

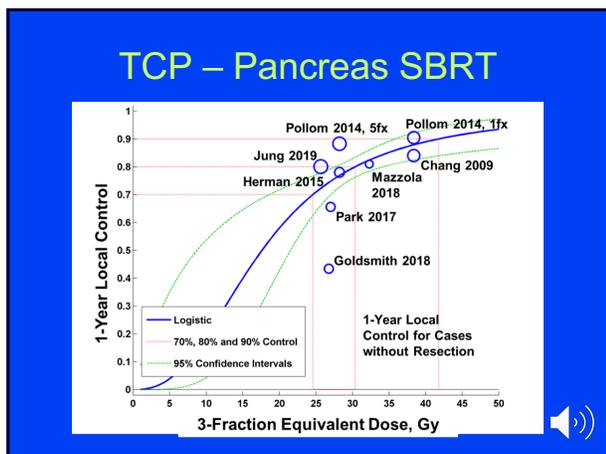
What Dose/Fractionation for Tumor control?

- Location.
- Radiosensitivity
- Organs at Risk
- Image guidance.
- Respiratory motion management

33



40



41

TCP – Pancreas SBRT

Number of Fractions	Total Dose (Gy)	3-Fraction Equiv. Dose (Gy)	1 Year LC without Surgery	1 Year LC with Surgery
1	25	38.4	88%	92%
3	36	36	86%	92%
3	30	30	79%	92%
1	20	30	79%	92%
5	33	28.2	77%	91%
5	30	25.8	73%	-
3	24	24	69%	-
5	25	21.7	63%	-
1	15	21.7	63%	-

42

HyTEC Pancreas TCP

HyTEC: Organ-Specific PaperHyTEC: Pancreas TCP

Maximizing Tumor Control and limiting complications with SBRT for Pancreatic Cancer

Anand Mahadevan, M.D., Shalini Moningi, M.D., Jimm Grimm, Ph.D., X. Allen Li, Ph.D., Kenneth M. Forster, Ph.D., Manisha Palta, M.D., Phil Prior, Ph.D., Karyn A. Goodman, M.D., M.S., Amol Narang, M.D., Dwight E. Heron, M.D., MBA, FACRO, FACR., Simon S. Lo, M.D., James Urbanic, M.D., Joseph M. Herman, MD., M.Sc. MSHCM



43

NTCP Grade 3+ Duodenal Toxicity

Table All Grade 3-4 Complications, Sorted by Fiducials and $D_{50\%}$

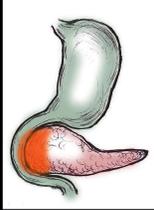
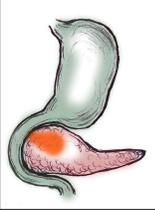
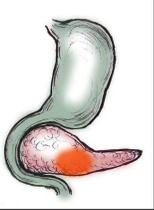
Endpoint	CTCAE v3 Grade	Total Equivalent Dose in 3 Fractions, Gy						Number of Fiducials
		$D_{50\%}$	$D_{10\%}$	$D_{30\%cc}$	$D_{5\%cc}$	$D_{1\%cc}$	$D_{0.035\%cc}$	
Duodenal stricture	4	1.8	6.0	4.2	6.8	8.3	11.2	1
Duodenitis	3	6.4	14.2	8.5	16.5	26.7	34.6	1
Bleeding	3	8.6	18.5	17.3	26.6	28.3	29.6	1
Obstructive jaundice	3	9.4	18.3	15.7	21.1	22.6	23.8	4
Fatigue and diarrhea	3	8.1	17.0	10.7	21.4	29.0	35.9	2
Duodenal hemorrhage	3	10.7	21.5	16.5	25.7	27.7	29.4	3
Duodenal stricture	4	11.1	23.6	13.8	26.0	29.1	31.6	3

*This patient experienced both grade 3 fatigue and grade 3 diarrhea. CTCAE, Common Terminology Criteria for Adverse Events



44

Tolerance Based Approach

800 cGy x 3 (total dose 2400 Gy)	1000 cGy x 3 (total dose 3000 Gy)	1200 cGy x 3 (total dose 3600 Gy)
		



45

Thank you



52
