

Pancreatic Cancer radiotherapy

PATIENT'S GUIDE

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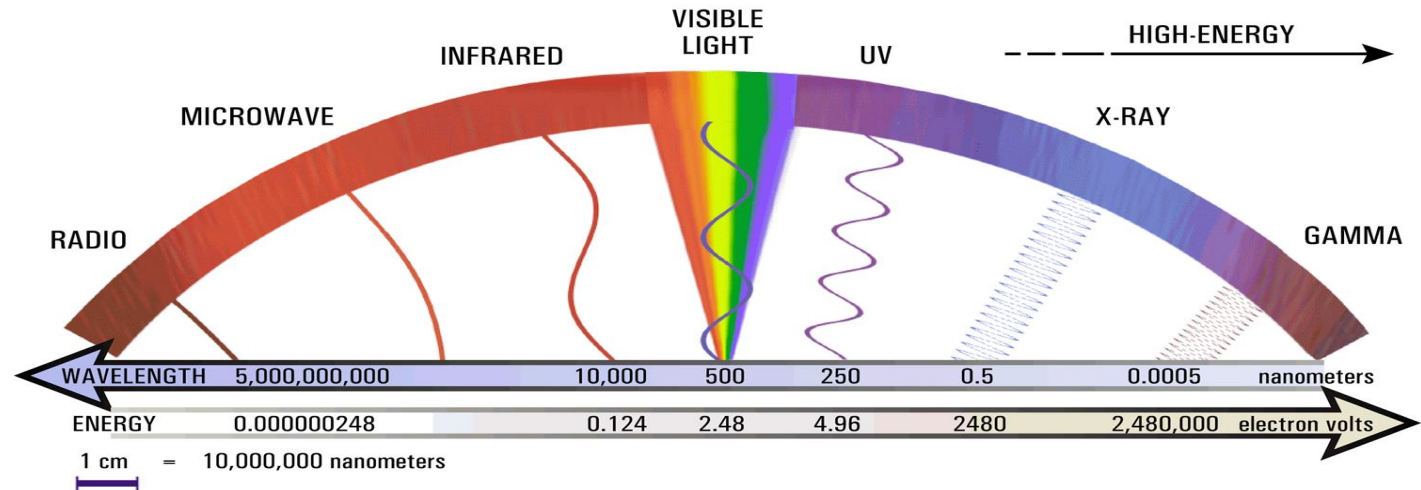


THE ROLE OF RADIOTHERAPY IN PANCREATIC CANCER

- Borderline resectable
- Locally advanced
- Adjuvant
- Palliative (pain, mass effect)
 - Coeliac axis SBRT
 - Symptomatic pancreatic tumour for SBRT
 - Metastatic sites

What is radiotherapy

High energy XR



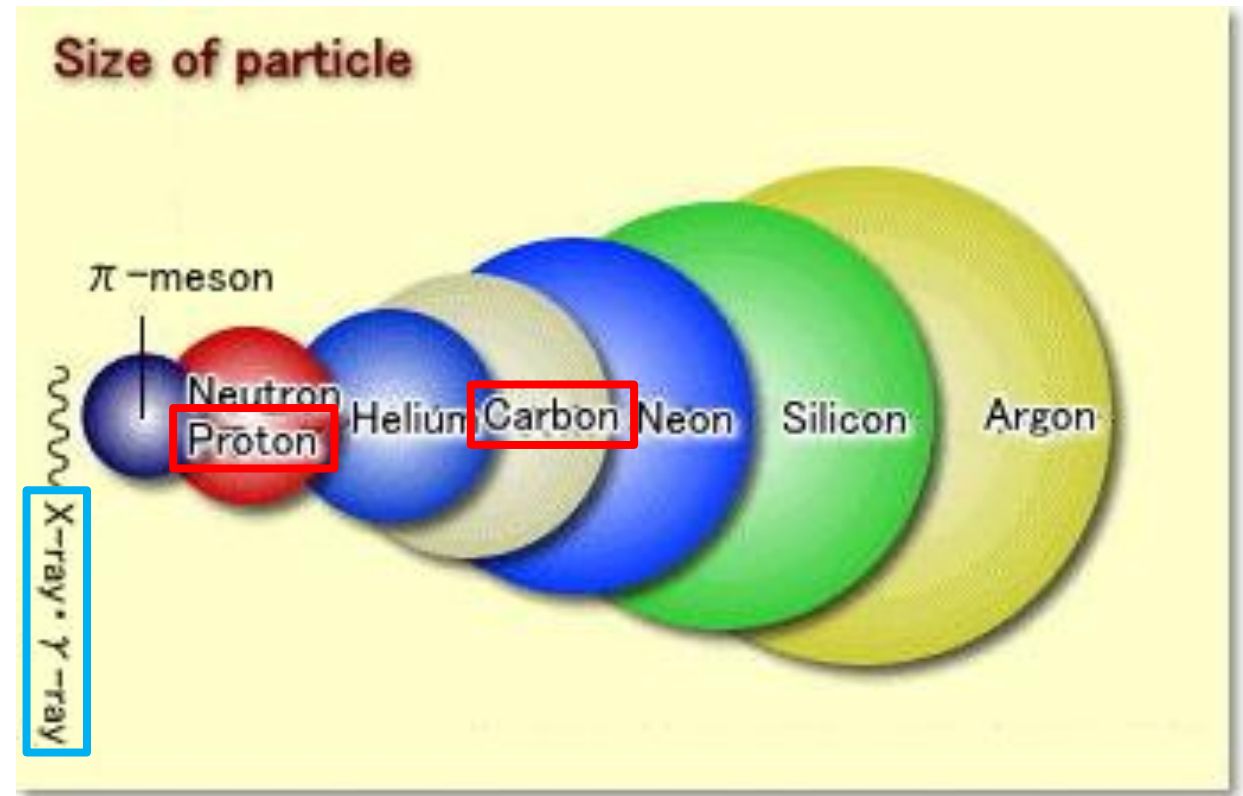
What is particle therapy?

Conventional radiotherapy

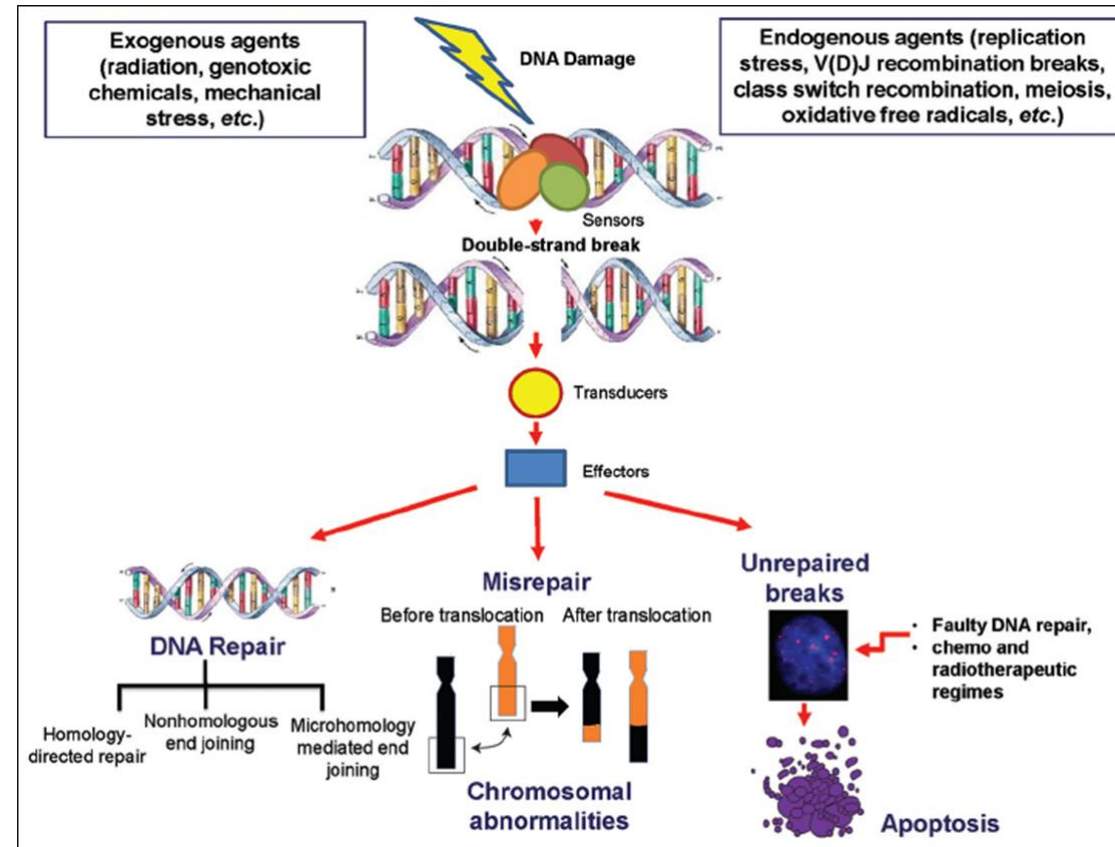
- X-rays, γ -rays
- Waves of light
 - Electric charge (-)
 - Mass (-)

Particle therapy

- Protons, carbon ions
- Particles of ion
 - Electric charge (+)
 - Mass (+)



How Radiotherapy Works



Radiotherapy process

Consultation

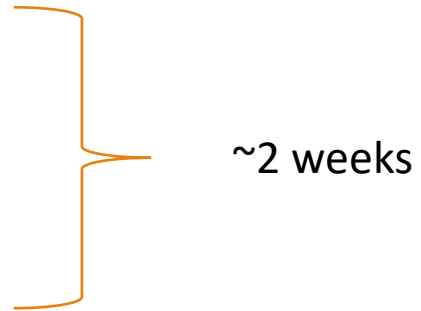
Sedation

Immobilization

Simulation

Planning

Delivery



Schedule

1st week | 2nd week | 3rd week | 4th week | 5th week | 6th week | 7th week



5 times a week

Neoadjuvant 5 weeks

Radical ablative radiotherapy : 5-6 weeks

SBRT or palliative treatment 1-2 weeks

Treatment fractionations

For neoadjuvant chemoradiation, RT dose generally consists of 45–54 Gy in 1.8–2.0 Gy fractions.

For unresectable ablative radiotherapy, there are limited data to support a specific RT dosing for SBRT; SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–50 Gy) have been reported.

More protracted courses delivering high doses through a hypofractionated approach (67.5 Gy in 15 fractions or 75 Gy in 25 fractions) are also acceptable.

Metastatic sites: 1-2 weeks

SBRT for pain: 1 week

Immobilization and simulation

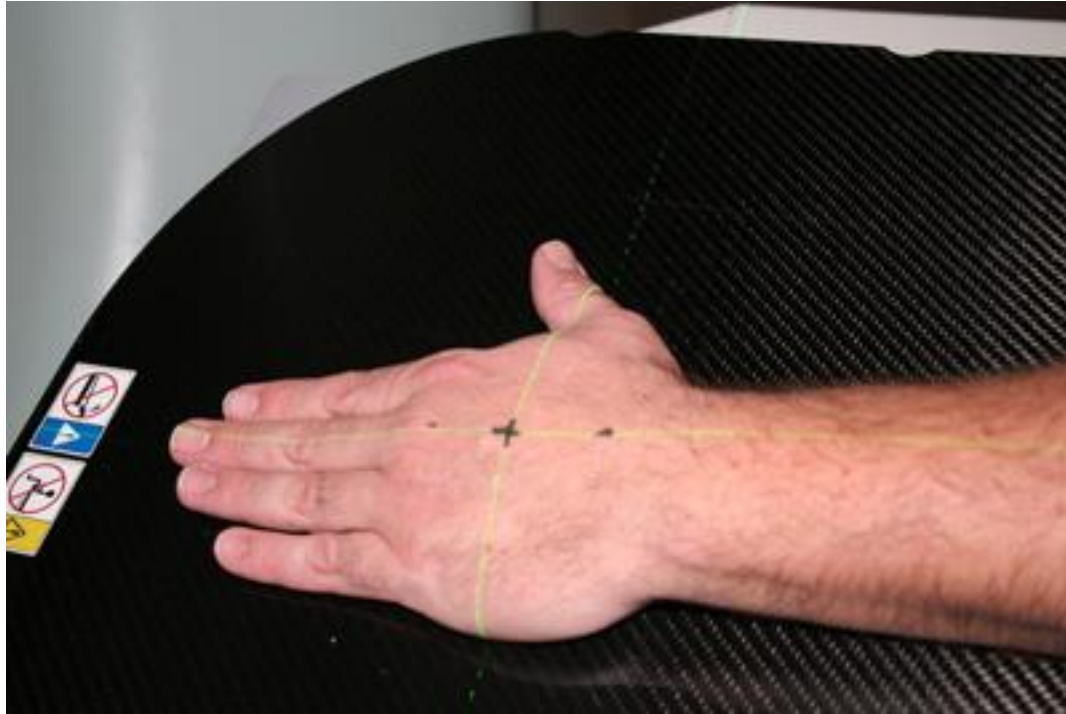


Source: www.qfix.com



www.civcort.com

Tattoo



www.oncolink.org



Community.macmillian.org.uk

Treatment room



Varian probeam

Anatomical Staging Pancreas Cancer

- cTNM not used in daily practice
 - cT: size, often isodense and poorly demarcated
 - cN: accuracy of coin toss
- Localized pancreas cancer staging based on vascular contact on CT

STAGE	VENOUS	ARTERIAL	TREATMENT
Resectable	<180	None	Upfront surgery
Borderline resectable	Reconstructible	SMA/CA<180, any CHA	Neoadjuvant
Locally advanced	Unreconstructible	SMA/CA>180	Induction

NCCN.org – version 2.2024

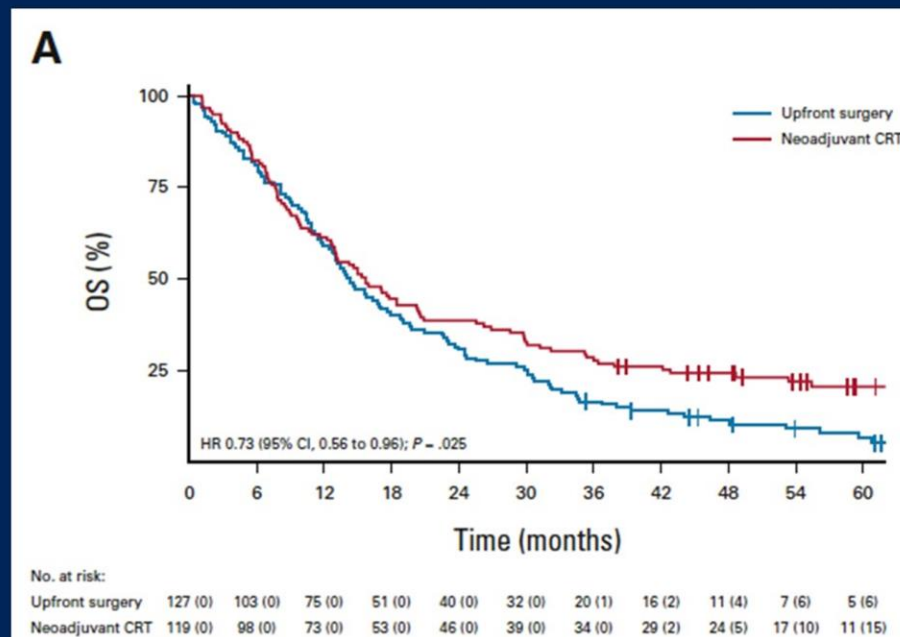
PREOPANC Trial - Results

Median 16 vs 14 months

HR 0.73 (0.56-0.96) – p=0.025

5-year OS 20.5% vs 6.5%

NNT of 7



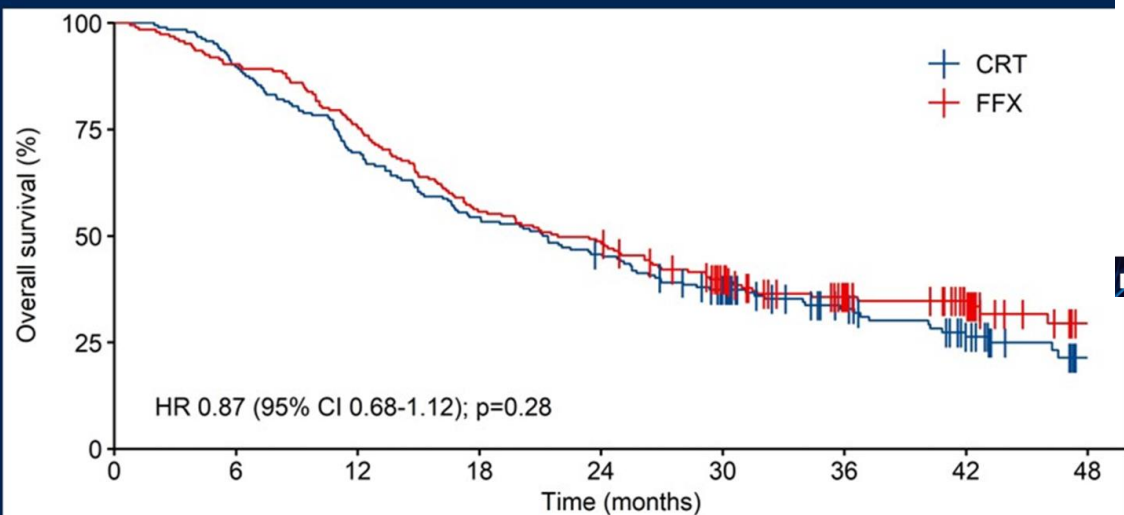
Gem + 36Gy/15#
Vs
Upfront + gem

Versteijne, J Clin Oncol 2020;38(16):1763

Versteijne, J Clin Oncol 2022;40(11):1220

PREOPANC 2

PREOPANC-2



	0	6	12	18	24	30	36	42	48
Number at risk									
CRT	184	165	128	100	83	61	39	24	7
FFX	185	167	140	103	90	64	43	28	9

Sohal, JAMA Oncol 2021,7(3);421
Groot Koerkamp, Ann Oncol 2023;34(S2):S1323

	FOLFIRINOX	GEM-CRT	P-value
ypN0	47%	58%	<0.01
ypN1	33%	35%	
ypN2	20%	7%	
R0	61%	67%	0.28
Complete PR	11%	5%	0.26

	FOLFIRINOX	GEM-CRT	P-value
SAE	49%	43%	0.26
Toxic death	2 (1%)	1 (1%)	0.56
Grade 3-4 AE	67%	60%	0.16
Diarrhea	23%	0%	<0.001
Fatigue	5%	3%	0.42
Febrile neutropenia	6%	1%	0.02
Neutropenia	25%	22%	0.51

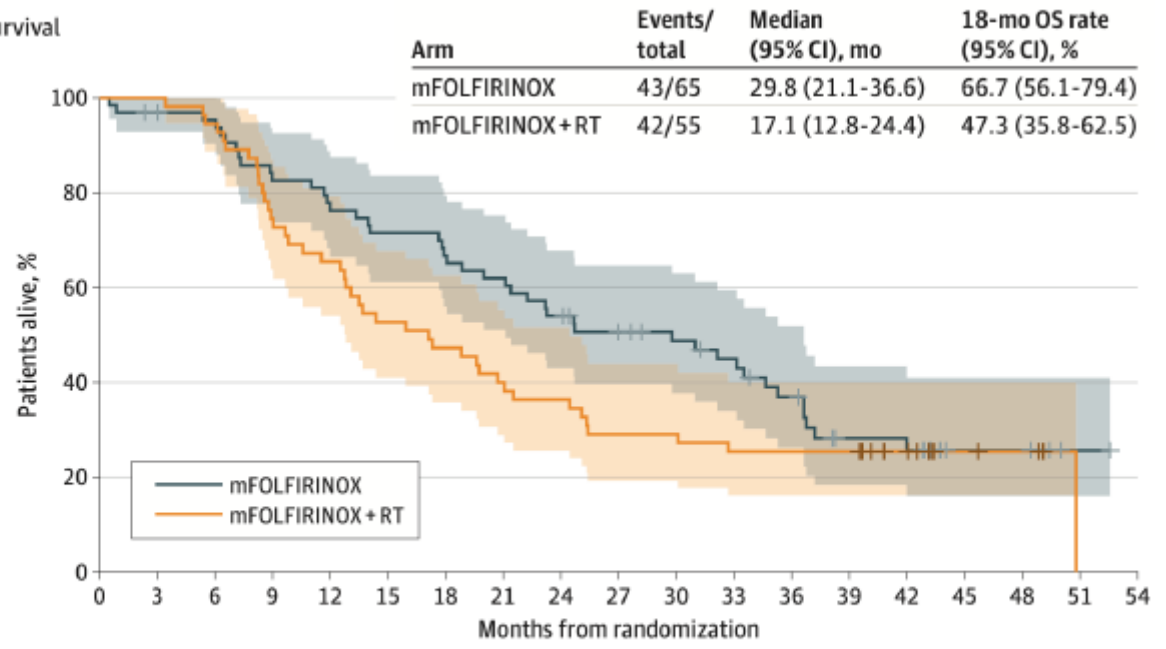
GRADE 3-4

Refresher Course | April 17-19

#Refresher24

Gem+36Gy RT
Vs
Folfolrinox

A Overall survival



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
mFOLFIRINOX	65	62	60	52	48	45	42	39	34	29	26	23	18	11	10	4	4	1	0
mFOLFIRINOX+RT	55	55	52	41	36	29	26	22	20	16	16	14	14	14	9	4	3	0	0

5 fractions
SBRT

JAMA Oncology | **Original Investigation**

Efficacy of Preoperative mFOLFIRINOX vs mFOLFIRINOX Plus Hypofractionated Radiotherapy for Borderline Resectable Adenocarcinoma of the Pancreas
The A021501 Phase 2 Randomized Clinical Trial

RCTs for Radiation of Pancreas Cancer

RCT	Setting	Sample size	OS
GITSG	Adjuvant	43	better
ESPAC-1	Adjuvant	289	worse
EORTC-40891	Adjuvant	218	same
EORTC-40013	Adjuvant	90	same
LAP-07	LAPC	269	same
Alliance A021501	BRPC	126	worse

- PREOPANC trials didn't investigate *additional* benefit of RT

Kaiser, Arch Surg 1985;120(8):899
 Neoptolemos, N Eng J Med 2004;350:1200
 Van Laethem, J Clin Oncol 2010;28:4450
 Smeenk, Ann Surg 2007;246(5):734
 Hammel, JAMA 2016;315(17):1844
 Katz, JAMA Oncol 2022;8(9):1257

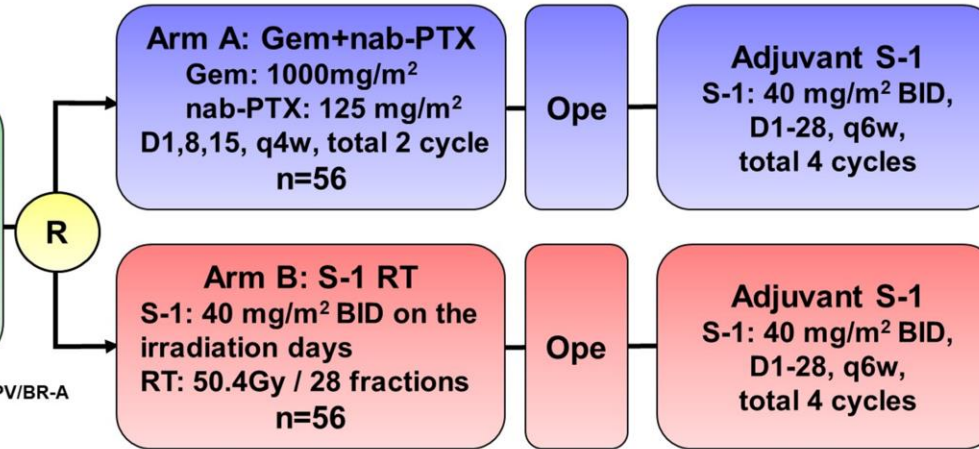
Older studies

Trial design of GABARNANCE

Key eligibility

- Histologically proven adeno(squamous)carcinoma
- Centrally-confirmed BRPC
- Age 20 to 79 years
- Performance status 0-1
- No prior treatment for BRPC

Stratification factor: Institution, CA19-9, BR-PV/BR-A



Primary endpoint:

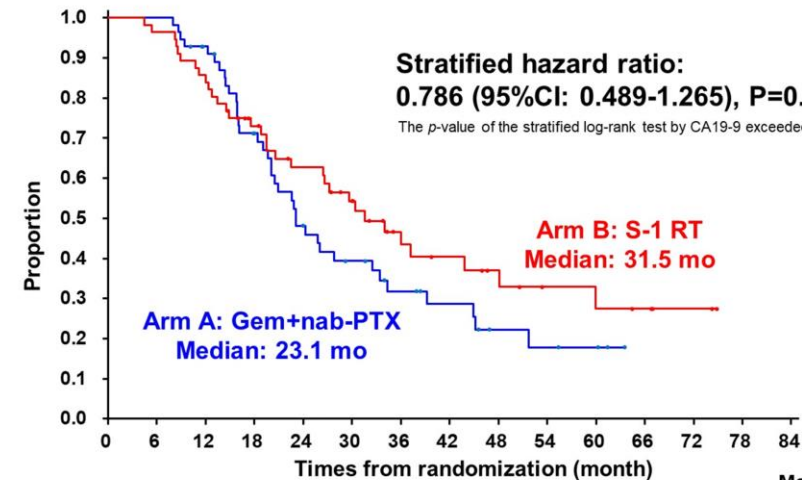
Phase II part: R0 resection rate

Phase III part: Overall survival (OS)

Secondary endpoints of phase III part:

Progression-free survival (PFS), R0 resection rate, objective pathological response rate, adverse events, treatment completion

Overall survival



Median follow-up period:
22.7 mo (IQR, 14.8-34.7 mo)

Objective response rate, R0 resection rate, and pathological response rate by neoadjuvant treatment

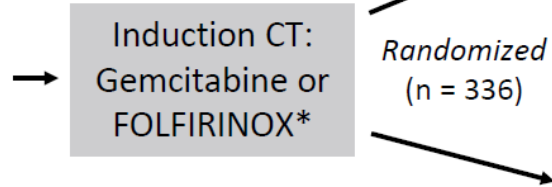
	Arm A: Gem+nab-PTX (n=56)		Arm B: S-1 RT (n=56)		p-value
CR	0		0		
PR	9		5		
SD	44		48		
PD	2		3		
NE	0		0		
Missing	1		-		
Objective response rate (95%CI)	16.1%	(7.6-28.3)	8.9%	(3.0-19.6)	0.3922
R0 resection rate (95%CI)	60.7%	(46.8-73.5)	57.1%	(43.2-70.3)	0.8478
Pathological response rate (95%CI)	14.3%	(6.4-26.2)	30.4%	(18.8-44.1)	0.0682

HOW ABOUT LOCALLY ADVANCED?

CONKO-007: Study Design

- Randomized phase III trial

Patients with unresectable locally advanced pancreatic cancer; no prior radiotherapy or chemotherapy; ECOG PS ≤ 2 (N = 402)



CRT: Gemcitabine + RT (50.4 Gy/28 fractions)[†]
(n = 167)

CT: Gemcitabine or FOLFIRINOX*
(n = 169)

Computed tomography scan for evaluation of resectability; if resectable, could proceed to surgery; if not, could receive additional chemotherapy

Survival same
RT increase margins –ve rates

*Gemcitabine 1000 mg/m²/d on Days 1, 8, 15, 29, 36, 43, 57, 64, and 71 or FOLFIRINOX on Days 1, 15, 29, 43, 57, and 71.

[†]Irradiation 28 x 1.8 Gy with total dose 50.4 Gy; gemcitabine 300 mg/m²/d on Days 1, 8, 15, 22, and 29 followed by gemcitabine 1000 mg/m²/d on Days 57, 64, and 71. [‡]Primary endpoint was changed from OS after interim analysis due to insufficient recruitment.

- **Primary endpoint:** R0 resection rate[‡]
- **Secondary endpoints:** OS, DFS, rate of resections, survival following resection
- **Median follow-up:** 55.13 mo

Unresectable

Maximal chemo > clinical trial > best supportive care

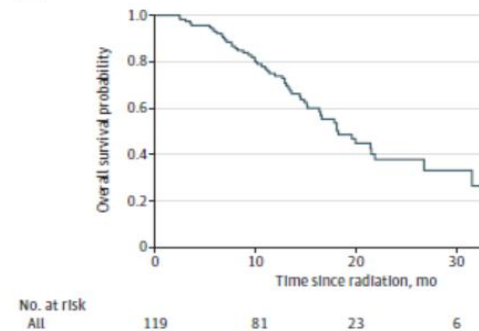
+/- ablative RT

- ❖ SBRT
- ❖ VMAT
- ❖ Protons

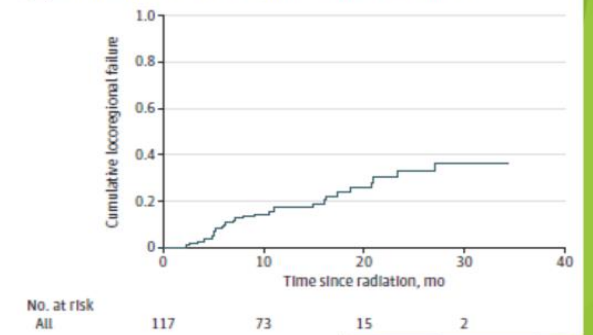
Definitive RT for unresectable

- ▶ SBRT
- ▶ MRI-guided
- ▶ Protons

A Overall survival from the time of A-RT



B Cumulative incidence of locoregional failure from the time of A-RT



JAMA Oncology | Brief Report

Association of Ablative Radiation Therapy With Survival Among Patients With Inoperable Pancreatic Cancer

Marsha Reyngold, MD, PhD; Eileen M. O'Reilly, MD; Anna M. Varghese, MD; Megan Fiasconaro, MSc; Melissa Zinovoy, MD; Paul B. Romesser, MD; Abraham Wu, MD; Carla Hajj, MD; John J. Cuaron, MD; Richard Tuli, MD, PhD; Lara Hilal, MD; Danny Khalil, MD, PhD; Wungki Park, MD; Ellen D. Yorke, PhD; Zhigang Zhang, PhD; Kenneth H. Yu, MD, MSc; Christopher H. Crane, MD

Japanese proton experience for unresectable

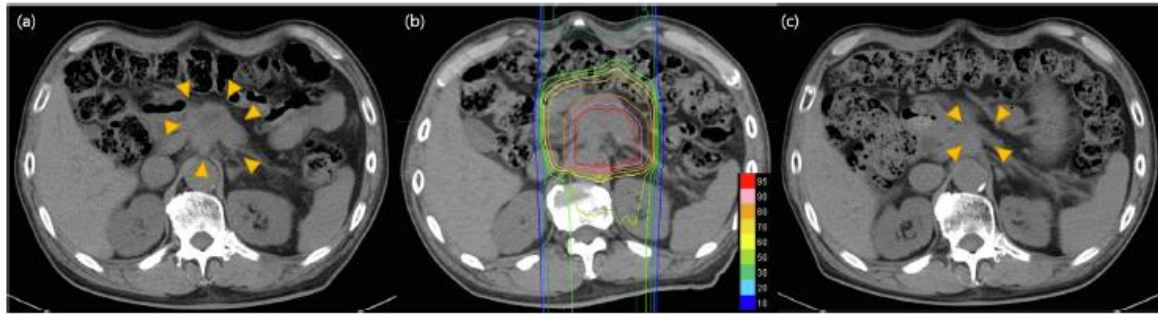
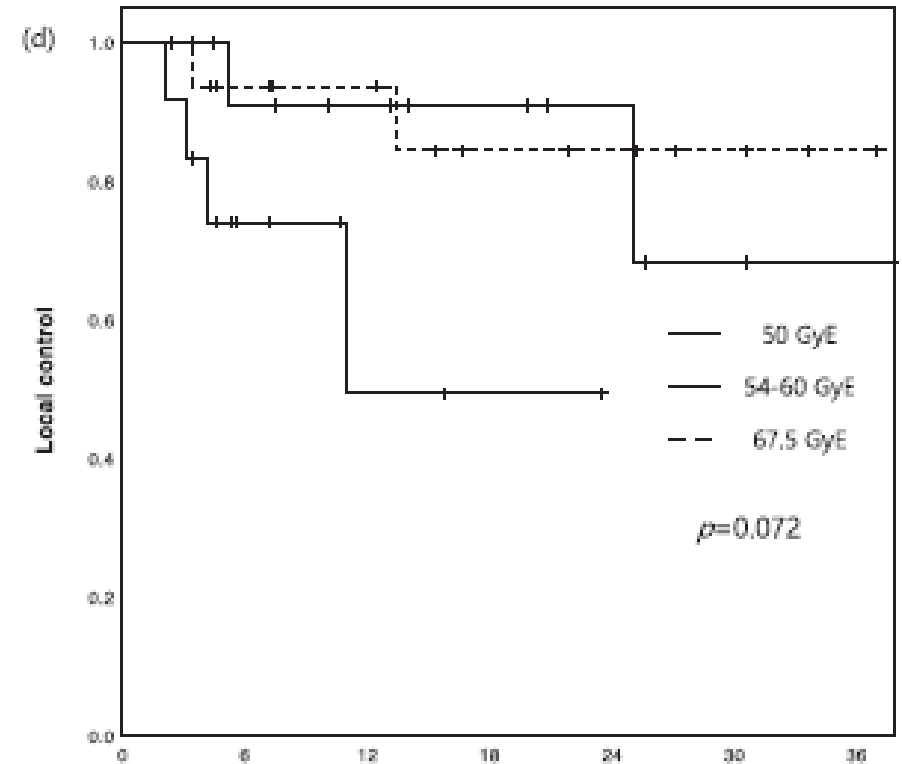


Fig. 3. Case presentation. 71-year old man with pancreatic cancer. (a) CT before treatment. Arrows indicate gross tumor volume. (b) Dose distribution image. Total irradiation dose is 67.5 GyE and isodose lines represent 95–10% of the isocenter dose from inside to outside. (c) CT 25 months after CCRT using proton beams. Arrows indicate a reduced tumor.

25# with TS-1
Local control 80%
with higher doses



	Number at risk						
	0	6	12	18	24	30	36
50 GyE	12	5	2	1	0	0	0
54-60 GyE	13	10	8	6	4	2	1
67.5 GyE	17	13	11	7	6	4	2

Neoadjuvant setting

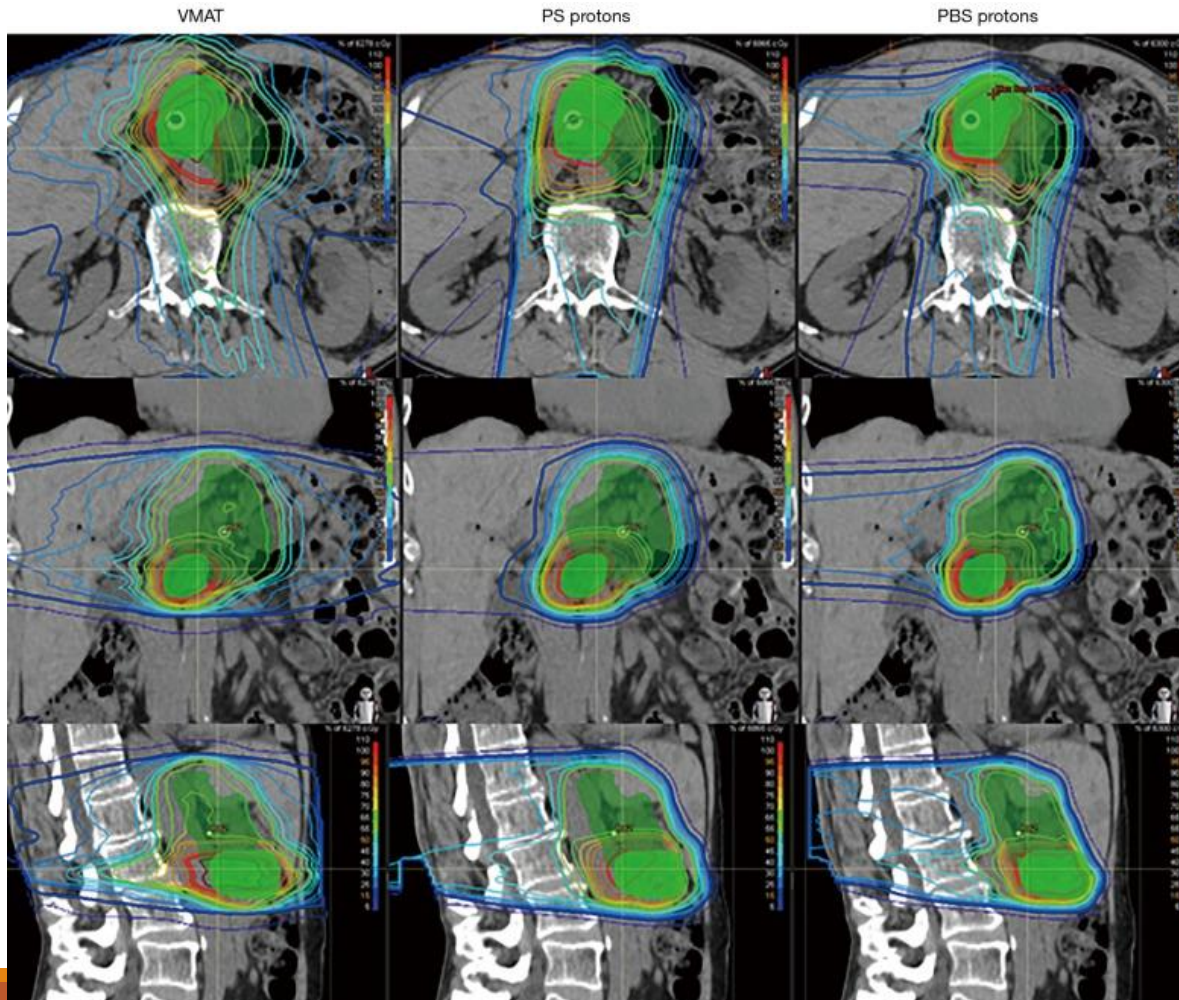
Borderline resectable >

- FFX alone or gem-36Gy (Dutch) or S1-50.4Gy (Jap)

Locally advanced >

- induction chemo > +/- RT
- 1/3 may go onto surgery to aim for R0
- Consider ablative radiotherapy if unresectable

VMAT versus Proton pencil beam



Lower doses to surrounding organs
But more expensive
No clinical trial to prove superiority
Case series with protons suggest fewer grade 3 toxicities
(Florida, NY, Tsukuba)

More physics uncertainties with protons
More expensive
Already quite safe with VMAT

Toxicities

Acute

- Marrow suppression
- Fatigue
- Nausea
- Diarrhea
- Gastritis and duodenitis
- Liver function derangement

Rare for grade 4 (severe)

Long-term

- Strictures (rare)

SUMMARY FOR ROLE OF RADIOTHERAPY

- Borderline resectable > neoadjuvant FFX or gem-36Gy (Dutch) or SI-50.4Gy (Jap)
- Locally advanced > induction chemo > +/- RT
- Adjuvant > if high risk
- Metastatic > given for pain or bleeding

CONTACT

- Questions
- Email ruxin.wong@proton.sg