KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

IASGO ICUR KSGC Korean Society of Gastrointestinal Cancer

Recent Updates in Management for Locally Advanced Pancreatic Cancer : *Radiation Oncology Perspective*

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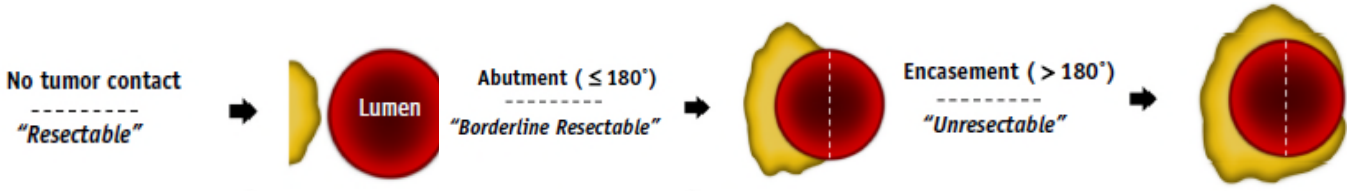
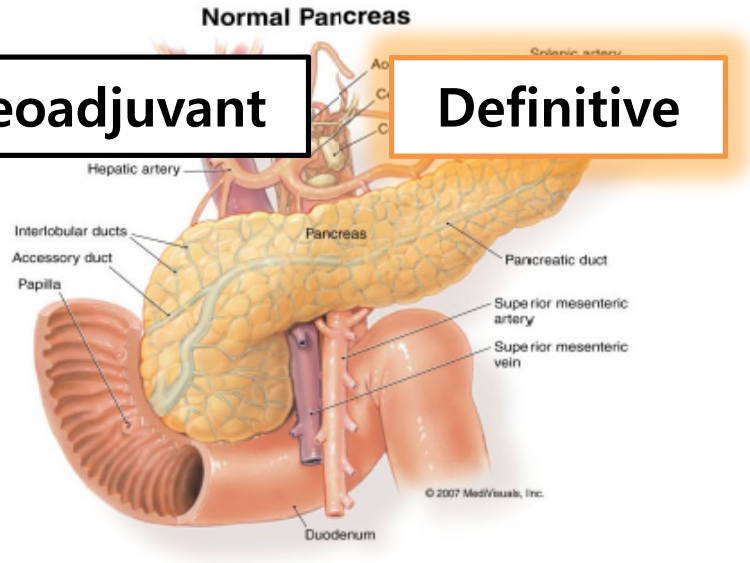
RT for Pancreatic Cancer



Resectable (20%)	Borderline resectable	Locally Advanced	Metastatic (53%)
Adjuvant	Neoadjuvant	Definitive	Palliative

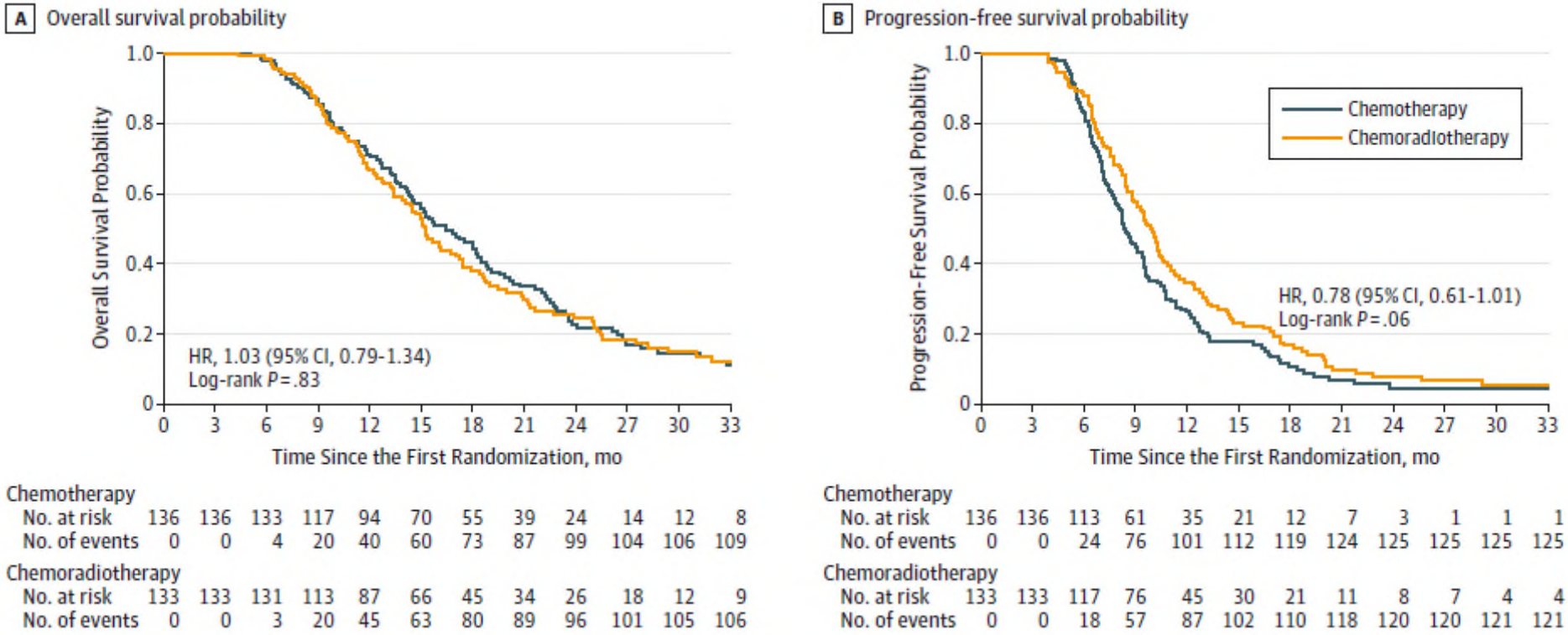


Locally Advanced PaC

Trial Acronym/Trial Name	Year Published	Reference	Treatment Arms	Median OS (months)	*P*	No. of Patients	
						Per Arm	Planned
Completed clinical trials							
GITSG	1988	[No authors listed][37]	RT (54 Gy) + fluorouracil, then SMF	9.7	.02	22	
			SMF alone	7.4		21	
ECOG	1985	Klaassen et al[38]	RT (40 Gy) + fluorouracil	8.3	> .05	47	
			Fluorouracil alone	8.2		44	
FFCD/SFRO	2008	Chauffert et al[36]	RT (60 Gy) + fluorouracil + cisplatin	8.6	.03	59	
			Gemcitabine alone	13		60	
ECOG 4201/Gemcitabine With or Without Radiation Therapy in Treating Patients With Pancreatic Cancer	2011	Loehrer et al[35]	RT (50.4 Gy) + gemcitabine	11.1	.017	34	
			Gemcitabine alone	9.2		37	
SCALOP	2013	Mukherjee et al[40]	Induction gemcitabine-capecitabine, then RT (50.4 Gy) + capecitabine	15.2	.012	36	
			Induction gemcitabine-capecitabine, then RT (50.4 Gy) + gemcitabine	13.4		38	
GERCOR-LAP-07-D07-1/Gemcitabine With or Without Capecitabine and/or Radiation Therapy or Gemcitabine With or Without Erlotinib in Treating Patients With Locally Advanced Pancreatic Cancer That Cannot Be Removed by Surgery	2013	Huguet et al[41]	Induction gemcitabine with or without erlotinib, then RT (54 Gy) + capecitabine	15.3	.83	136	
			Gemcitabine with or without erlotinib alone	16.5		133	

Heestand et al. J Clin Oncol 2015;33:1770

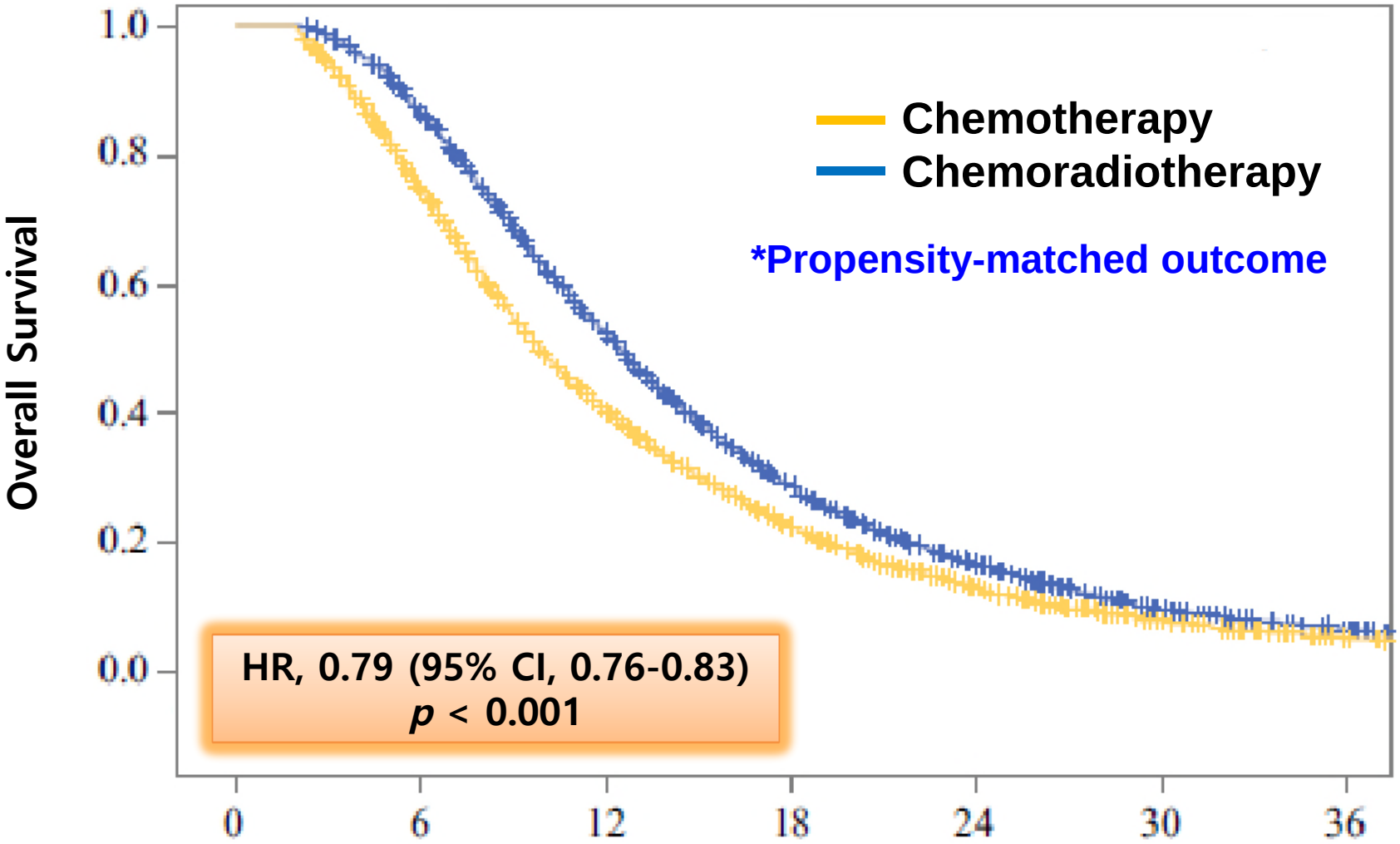
LAP-07



- LAPC with disease controlled after induction chemotherapy
- No significant difference in OS and PFS with CCRT compared with Chemotherapy alone

Hammel et al. JAMA 2016;315:1844

NCDB

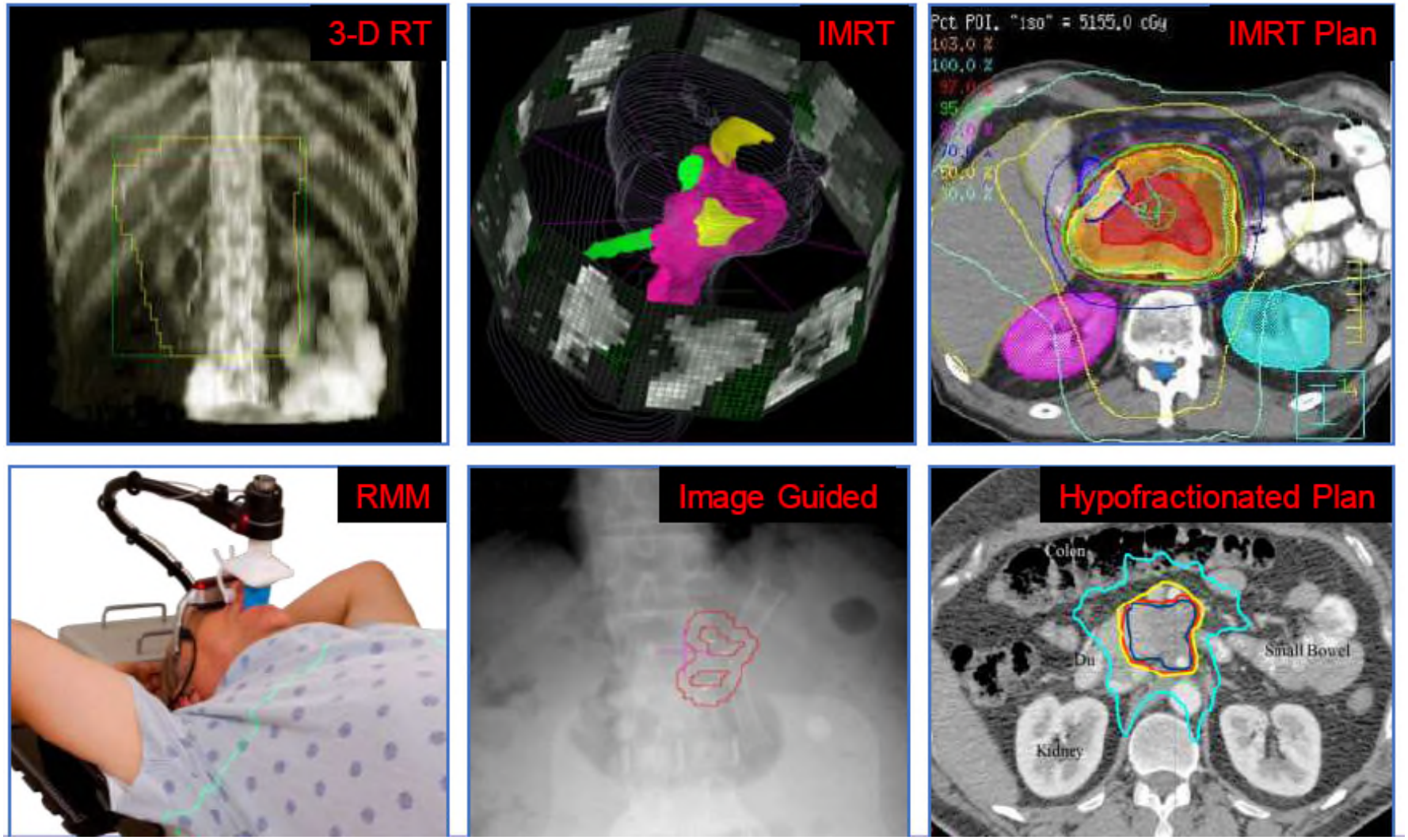


Zhong et al. Ann Surg Oncol 2018;25:1026

Why No Benefit of RT?

- Dose – insufficient dose d/t dose-limiting organs
- Toxicity – adjacent normal organs, more with combined chemotherapy
- Radioresistant – adenocarcinoma, intrinsic
- Frequent distant metastasis – local control less important
- Conflicting clinical evidences – study designs, statistical power

Evolution of Pancreas RT

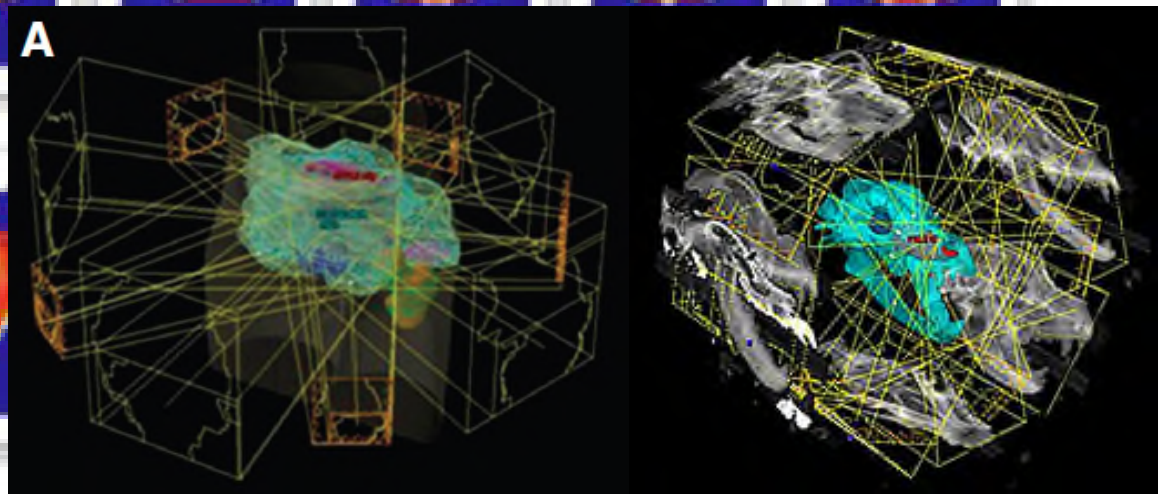


Courtesy by Dr. Manisha Palta, ASTRO 2017

Intensity Modulated RT

- **Intensity-modulated radiation therapy (IMRT)** is an advanced type of high-precision radiation that is the next generation of 3D-CRT.
- IMRT also improves the ability to conform the treatment volume to concave tumor shapes.

Beam Intensity Modulation



Details of 13 Original Studies Reporting IMRT and 7 Studies Reporting 3D-Conformal Planned Radiotherapy in Pancreatic Cancer.

Study	Median OS – resected R0	Median OS – resected R+	Median OS – non-resected	Median PFS – resected R0	Median PFS – resected R+	Median PFS – non-resected	Setting	Concurrent Chemotherapy	Dose in Gy	IMRT details	Toxicity scale
Intensity modulated radiotherapy											
Yovino 2011	24.8 months ("resectable")		9.7 months	17.5 months ("resectable")			Adjuvant/ definitive	Capecitabine or 5-FU	45 – 59.4	Inverse planned	CTC
Yovino 2012	25 months			15 months			Adjuvant	Capecitabine or gem	45 – 59.4	Inverse planned	n.a.
Bai 2003	Unknown/insufficient follow-up						Additive/ definitive	Gem or 5-FU	51 – 60	Inverse planned	CTC 2.0
Ben-Josef 2004	Unknown/insufficient follow-up						Adjuvant/ definitive	Capecitabine, partly celecoxib	45 – 55	n.a.	CTC 2.0
Milano 2004	14.3 months		9.3 months				Adjuvant/ definitive	5-FU	41.4 – 59.4	Inverse planned	CTC 2.0
Fuss 2007	10.8 months	10.2 months	10.0 months				Adjuvant/ definitive	Capecitabine or 5-FU or other	45 – 64	Inverse planned	RTOG
Ma 2010	Unknown/insufficient follow-up						Adjuvant	Capecitabine, erlotinib	45 – 50.4	n.a.	CTC 3.0
Patel 2011	15.6 months			10.5 months			Neoadjuvant	5-FU	45 – 50	Dose-painting	n.a.
Abelson 2012	20.4 months		7.7 months				Adjuvant/ definitive	Capecitabine or 5-FU	39.6 – 59.4	Inverse planned	n.a.
Ben-Josef 2012	Overall: 14.8 months; resected: 32 months						Definitive	Gem	50 – 60	n.a.	n.a.
Tuncer oglu 2012			11.6 months			5.9 months	Definitive/ neoadjuvant	Gem	45 – 54	Dose-painting with SIB	CTC 4.0
Pipas 2012	24.3 months (including additional 10 Gy IORT)		10.0 months				Neoadjuvant	Cetuximab, gem	45 – 54	SIB	CTC 3.0
Herman 2013	24.4 months						Adjuvant	Capecitabine, erlotinib	45 – 50.4	n.a.	CTC 4.0
3D-conformal planned radiotherapy											
Loehrer 2011			11.1 months			6.0 months	Definitive	Gem	39.6 – 50.4	3D QA	n.a.
Regine 2008	Pancreatic head tumors: 20.5 months (Gem), 16.9 months (5-FU)						Adjuvant	5-FU or gem	45 – 50.4	⩾3 fields	RTOG
Chauffert 2008			8.6 months				Definitive	5-FU, cisplatin or gem	60	n.a.	CTC 3.0
Golcher 2014	25 months						Neoadjuvant	Gem, cisplatin	50.4 – 55.8	3-5 fields	CTC 2.0, RTOG
Huang 2011			12.5 months (Gem), 10.2 months (5-FU)				Definitive	5-FU or gem	24 – 63	n.a.	CTC 4.0
Van Laethem 2010	24.3 months						Adjuvant	Gem	50.4	n.a.	CTC 2.0
Topkan 2012			15.2 months			7.3 months	Definitive	5-FU	50.4	4 fields	n.a.

IMRT (Median Survival)
R0 10.8–25 Months
LA 7.7–11.6 Months

3D-CRT (Median Survival)
R0 16.9–25 Months
LA 8.6–15.2 Months

Abbreviations: CTC, National Cancer Institute – Common Toxicity Criteria; n.a., not available; QA, quality assurance; RTOG, Radiation Therapy Oncology Group; SIB, simultaneous integrated boost; 5-FU, fluorouracil; gem, gemcitabine.

Bittner et al. Radiother Oncol 2015;114:117

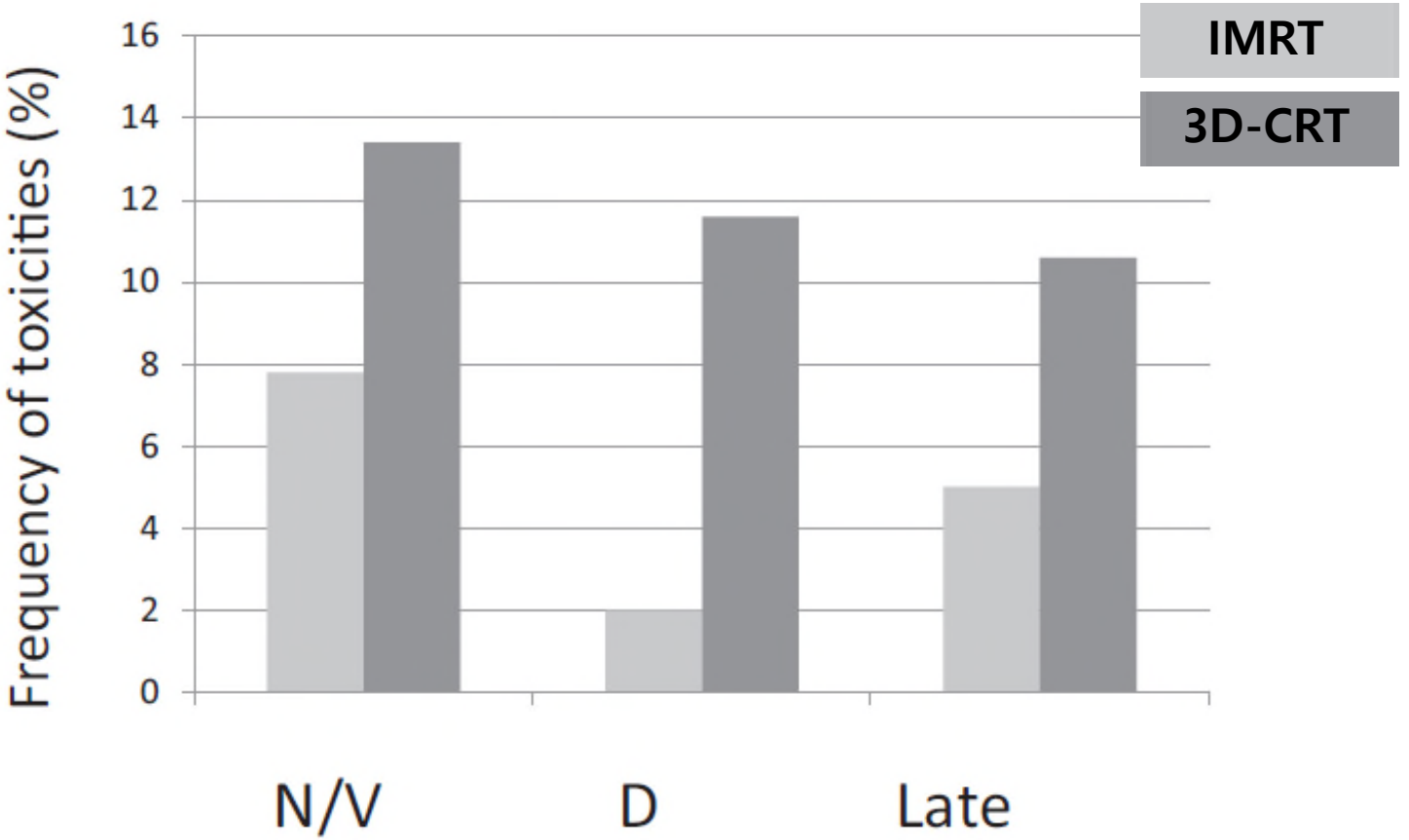


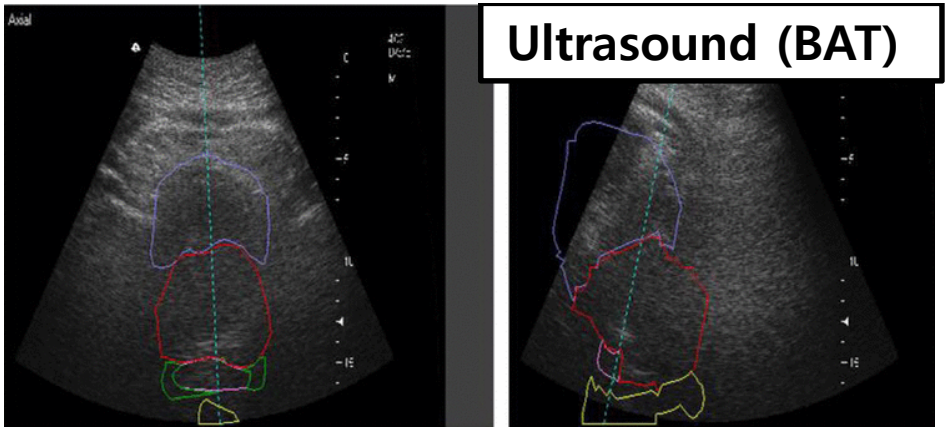
Fig. 1. Acute and late toxicity grade $\geqslant 3$ in percent for the trials included in this analysis comparing IMRT with 3D-radiotherapy, analysing for acute toxicities 446 vs. 747 patients and for late toxicities 381 vs. 207 patients, respectively. Abbreviations: N/V = nausea and vomiting; D = diarrhoea; 'Late' is for late gastrointestinal toxicities. The p-values from left to right $p < 0.001$, $p < 0.001$, and $p = 0.017$.

Bittner et al. Radiother Oncol 2015;114:117

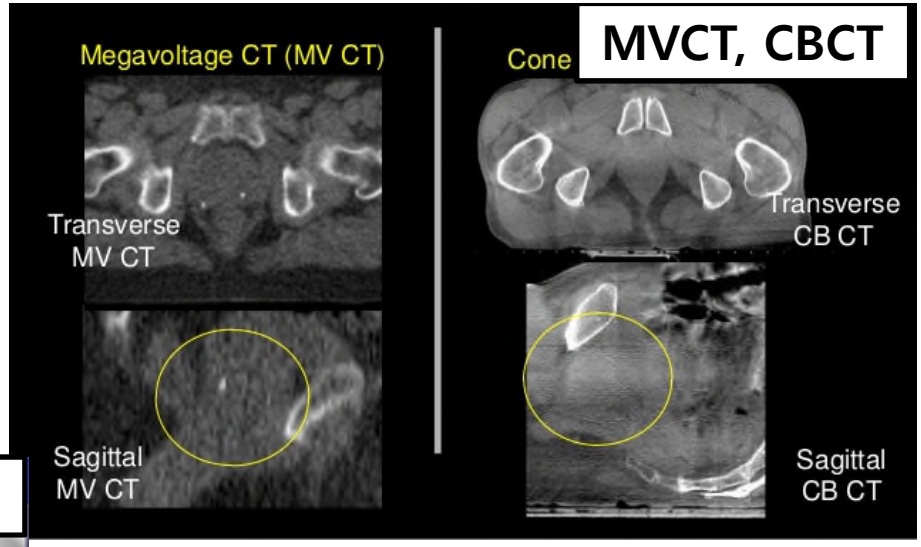
Image Guided RT

- **Image-guided radiation therapy (IGRT)** is the process of frequent two and three-dimensional imaging, during a course of radiation treatment, used to direct radiation therapy utilizing the imaging coordinates of the actual radiation treatment plan.
- Fluoroscopy, Digital X-ray, CT, Cone beam, MVCT, Optical tracking, MRI, Ultrasound, Electromagnetic transponders

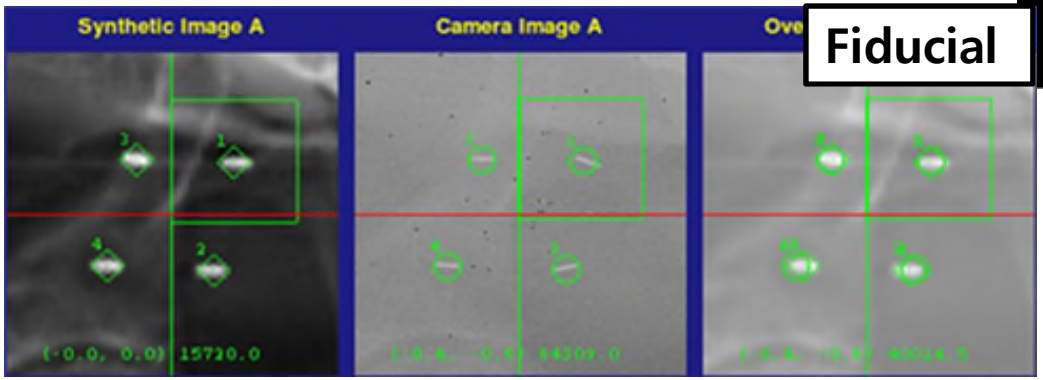
Ultrasound (BAT)



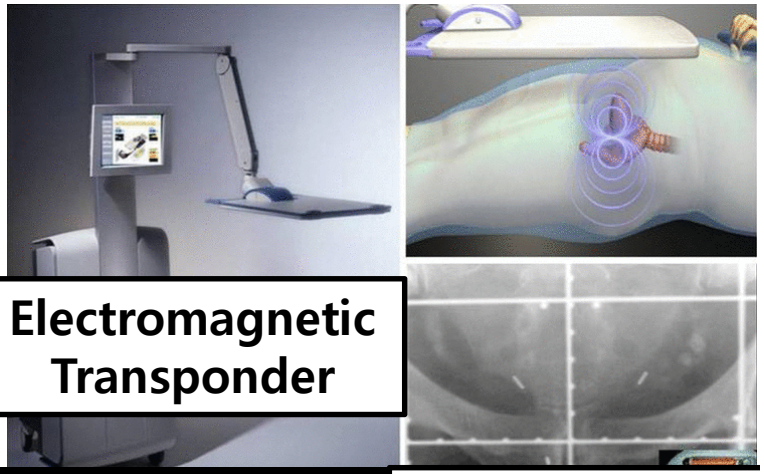
MVCT, CBCT

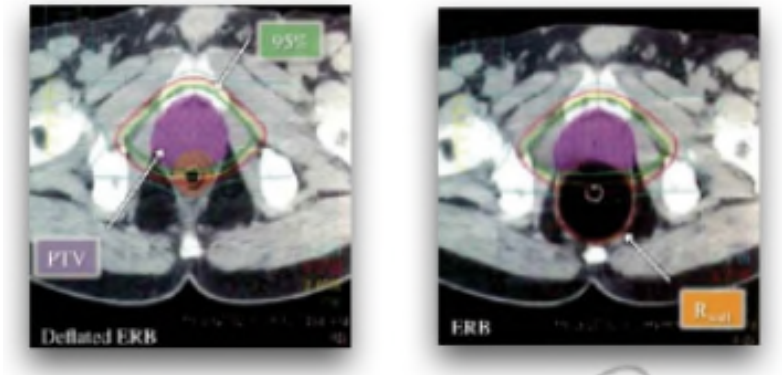


Fiducial

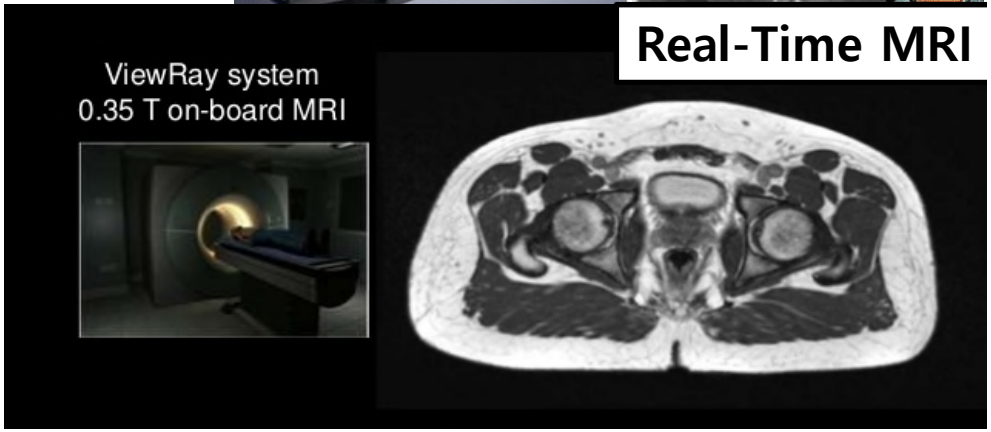


Electromagnetic Transponder



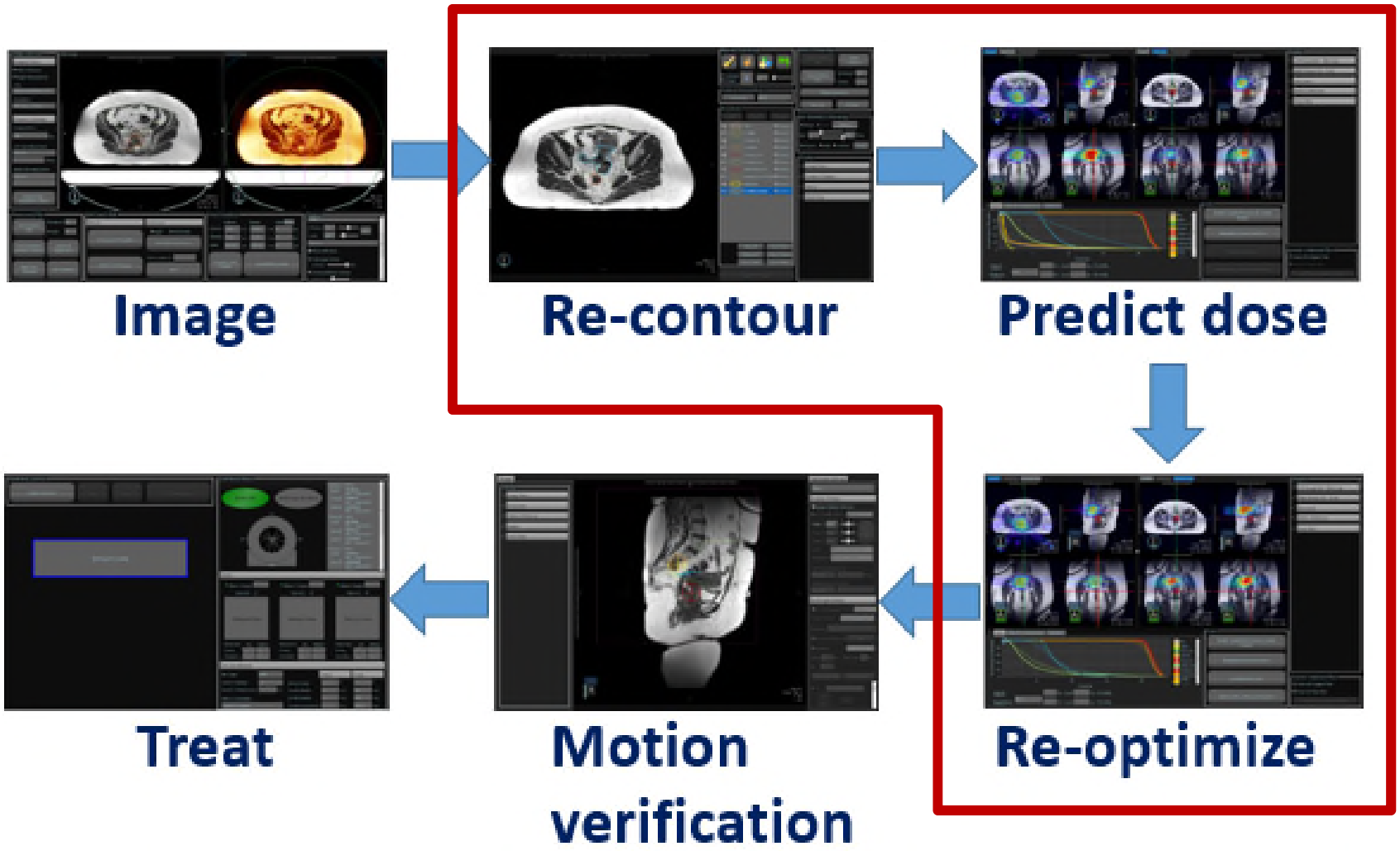


Real-Time MRI



Endorectal Balloon

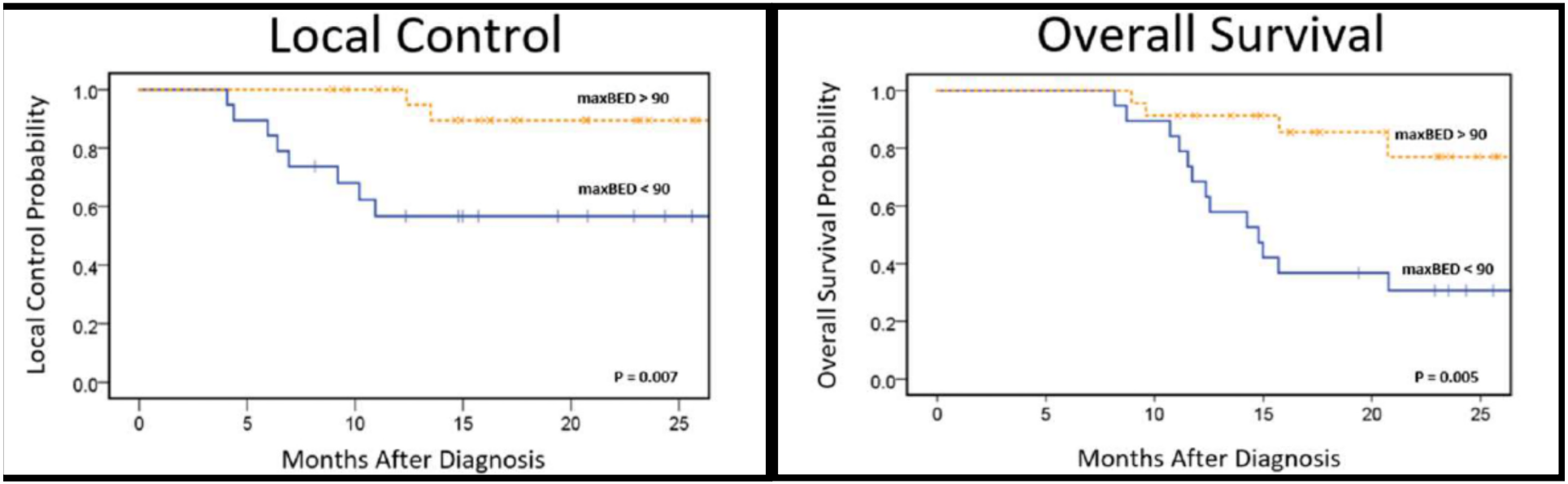
MRI Based Adaptation



Courtesy by Dr. Rudra and Parikh, ASTRO 2017

Preliminary Result
-Multicenter Study of MRg SBRT-

$maxBED_{10}$ > 90
$maxBED_{10}$ < 90

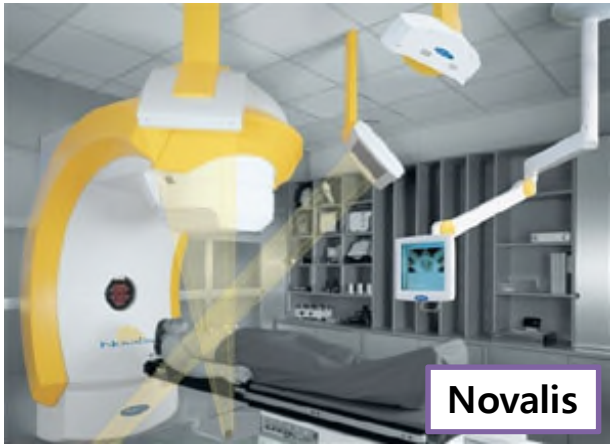


<Gr3+ GI Toxicity>
maxBED>90: 0%
maxBED<90: 15.8%

Courtesy by Dr. Joseph Herman, ASTRO 2017

Stereotactic Body RT

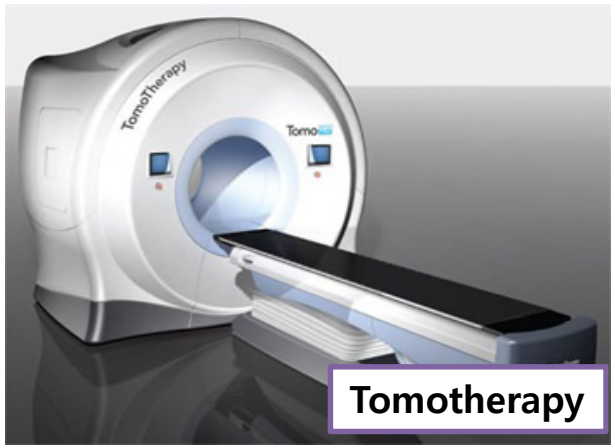
- **Radiosurgery** is surgery using radiation, that is, the destruction of precisely selected areas of tissue using ionizing radiation rather than excision with a blade.
- **Stereotactic Body RT**, high dose fraction of radiation, stereotactically directed to a extracranial region of interest

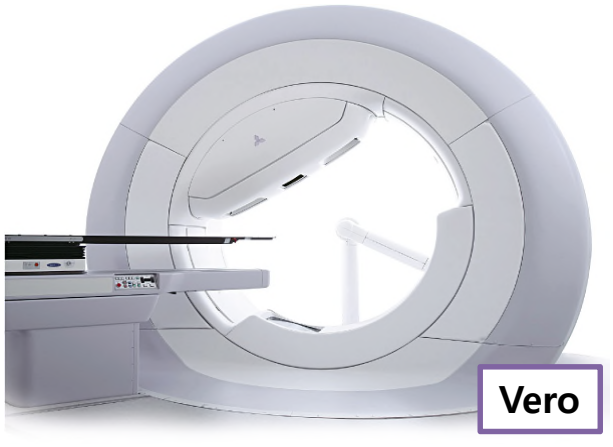

Novalis


Elekta Versa


Varian VitalBeam


Cyberknife M6


TomoTherapy
Tomotherapy


Vero


VIEWRAY
ViewRay (MRI-Cobalt)

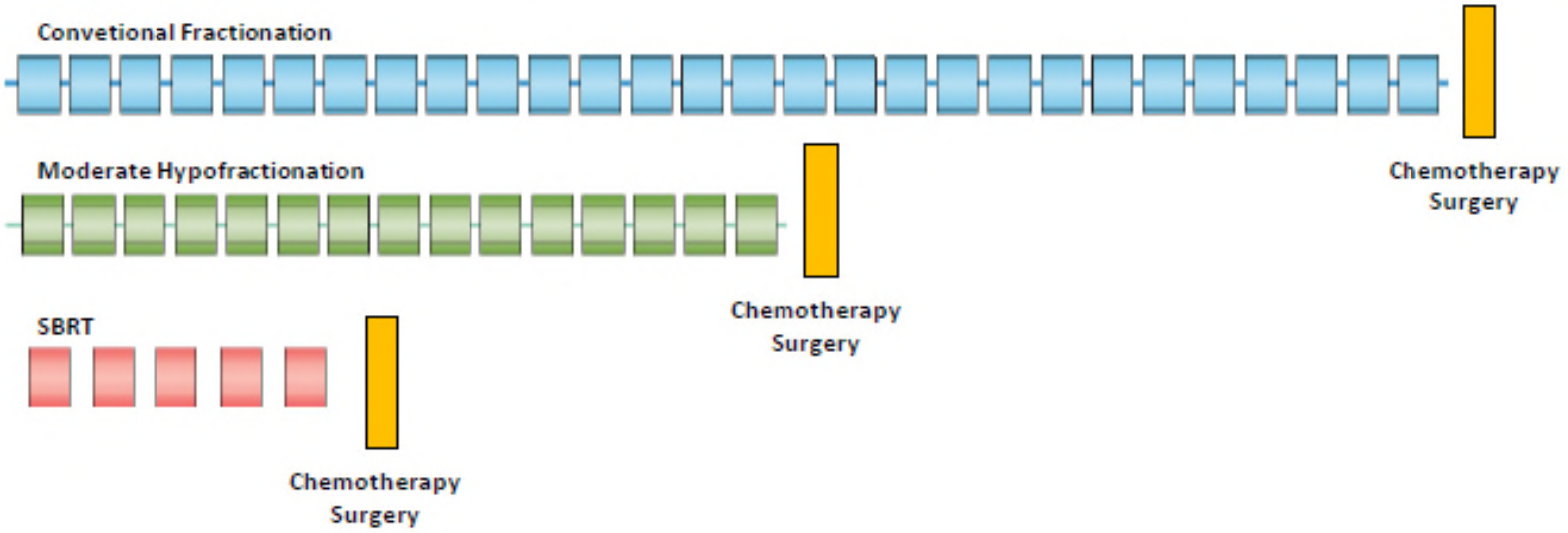

ProBeam (Varian Proton)


Mevion S250

Clinical Rationale of SBRT

(1) SBRT can be delivered as a hypofractionated regimen over **3-5 days** in comparison to **25-30 days** with conventional chemoradiation (CRT).

(2) SBRT allows for **good local control** while **limiting the delay of additional therapies** such as full-dose systemic chemotherapy or surgical resection

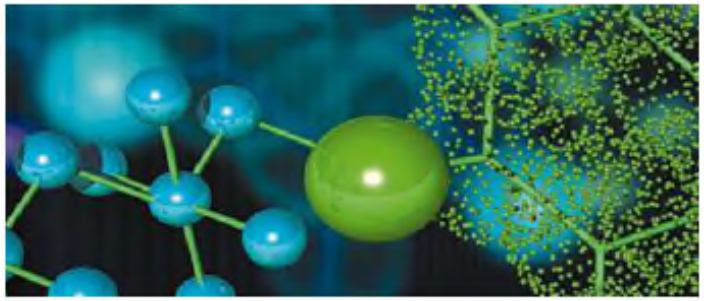


Rosati et al. Semin Radiat Oncol 2017;27:256

Clinical Rationale of SBRT

(3) SBRT results in **minimal acute side effects** and improves pain while preserving **quality of life.**

(4) The **radiobiology** of SBRT, along with the ability to **escalate the dose** to more than 50Gy at the tumor-vessel interface, may increase the likelihood of a margin-negative resection and decrease the risk of a subsequent local recurrence.




Courtesy by Dr. Marta Scorsetti, ASTRO 2017

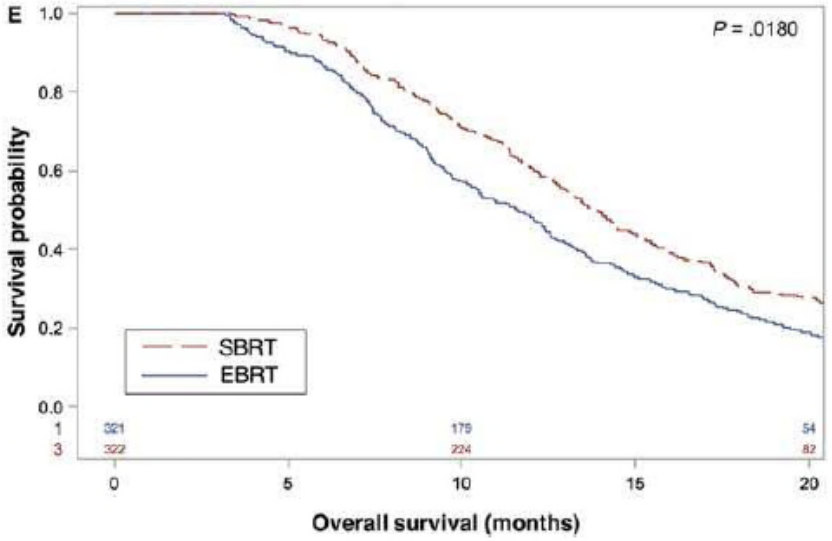
Rosati et al. Semin Radiat Oncol 2017;27:256

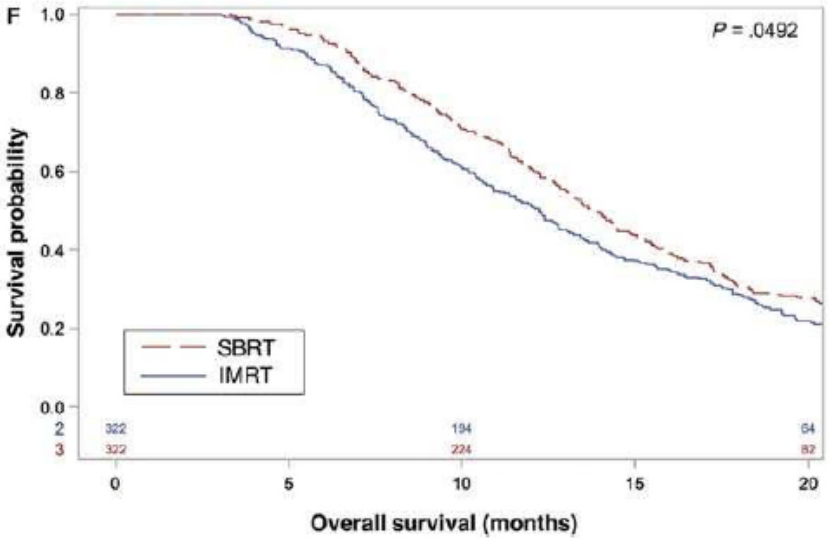
Author, Study, Year (Reference)	Patients (n)	SBRT Dose (Gy/fraction)	1-year FFLP (%)	PFS, months	OS, months	Acute GI toxicity (>G2)	Late GI toxicity (≥ G2)
Koong *et al*, Stanford phase I, 2004[10]	15	15-20 Gy/1 fr	77%	2	11 from diagnosis	33%	–
Koong *et al*, Stanford phase II, 2005[11]	19	25 Gy/1 fr	94%	4	8	12.5%	–
Hoyer *et al*, Danish phase II, 2005[12]	22	45 Gy/3 fr	57%	4.8	5.7 from diagnosis	79%	94%
Schellenberg *et al*, Stanford 2008[13]	16	25 Gy/1 fr	100%	9	11.4 from diagnosis	19%	47%
Chang *et al*, Stanford 2009[14]	77	25 Gy/1 fr	84%	–	11.4 from diagnosis	5%	13%
Schellenberg *et al*, Stanford phase II 2011[15]	20	25 Gy/1 fr	94%	9.2	11.8 from diagnosis	15%	20%
Polistina *et al*, Vicenza 2010[16]	33	30 Gy/3 fr	82.6%	7.3	10.6	0	–
Didolkar *et al*, Baltimore 2010[17]	85	15-30 Gy/3 fr	91.7%	–	18.6 from diagnosis; 8.6 from SBRT	0	22%
Mahadevan *et al*, Deaconess 2011[18]	39	24-36 Gy/3 fr	85%	15	20	41%	6%
Rwigema *et al*, Pittsburgh 2011[19]	71	18-25 Gy/1 fr	64.8%	–	10.3	0	10%
Gurka *et al*, 2013[20]	10	25 Gy/5 fr	40%	–	12.2	0	0%
Tozzi *et al*, Milano 2013[21]	30	36-45 Gy/6 fr	85%	8	11 from SBRT; 19.5 from diagnosis	20%	0%
Chuong *et al*, 2013[22]	16	25-50 Gy/5 fr	81%	–	15	0%	5.3%
Herman *et al*, phase II 2015[23]	49	33 Gy/5 fr	78%	7.8	13.9	12.2%	10.6%
Comito *et al.* 2017	45	45 Gy/6 fr	LAPC: 90%	LAPC: 8	LAPC: 13 from SBRT and 19 from diagnosis	29%	3%

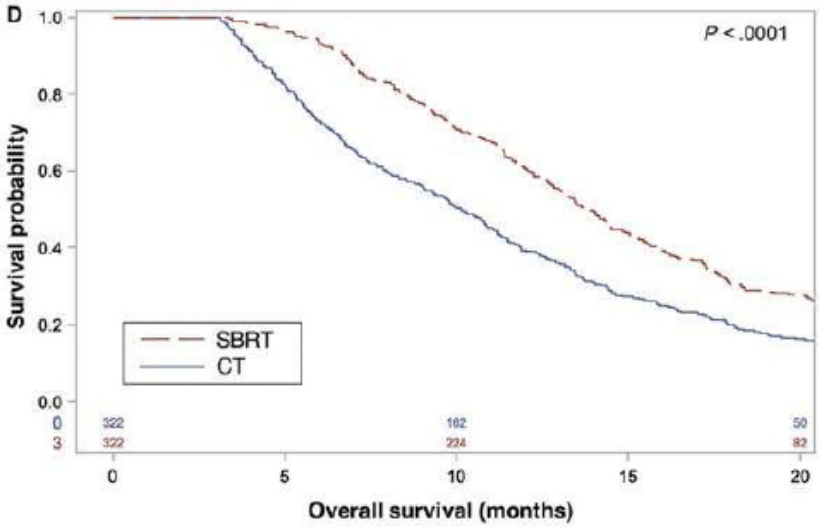
Abbreviations: FFLP, freedom from local progression; fr, fraction; GI, gastrointestinal toxicity; LAPC, locally advanced pancreatic cancer; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

Comito et al. Technol Cancer Res Treat 2017;16:1295

NCDB





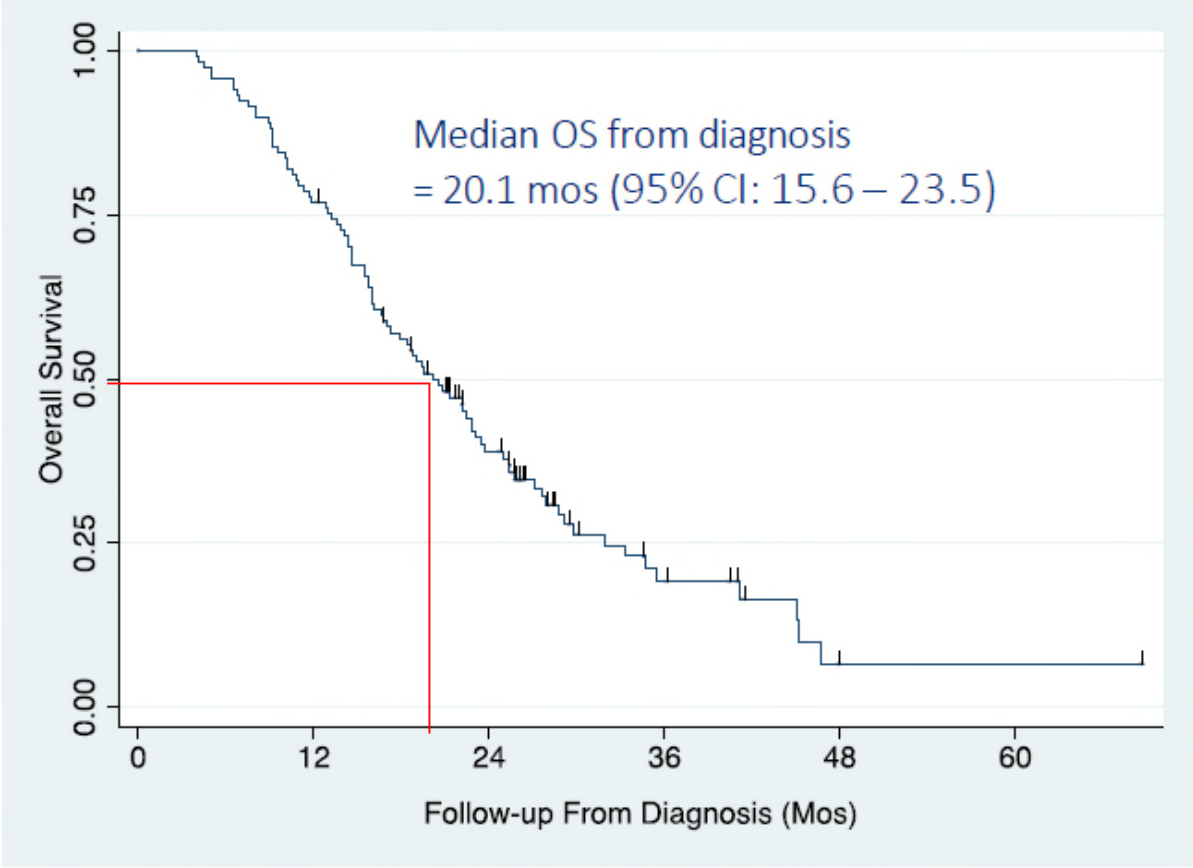


Median Survival
- **CTx alone 10.2M**
- **EBRT 11.6M**
- **IMRT 12.2M**
- **SBRT 13.9M**

Rosati et al. Semin Radiat Oncol 2017;27:256

Multi-Agent Chemo and SBRT

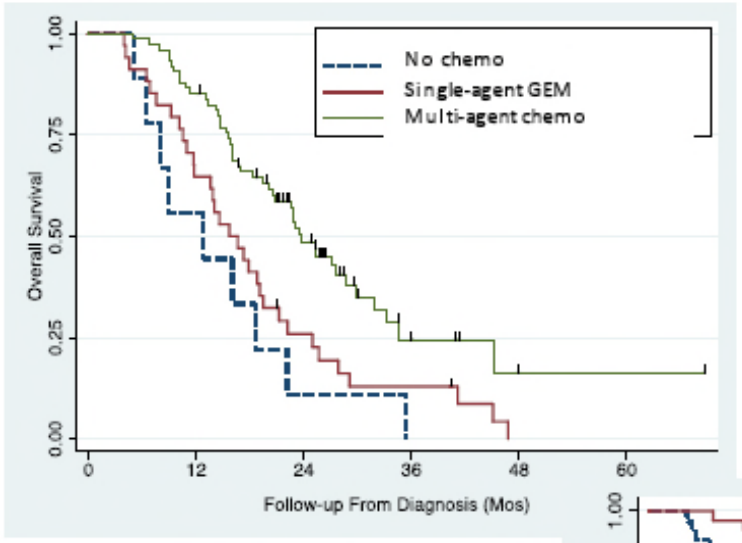
- 2010–2015
- N=117
- LAPC
- Definitive Chemo+SBRT

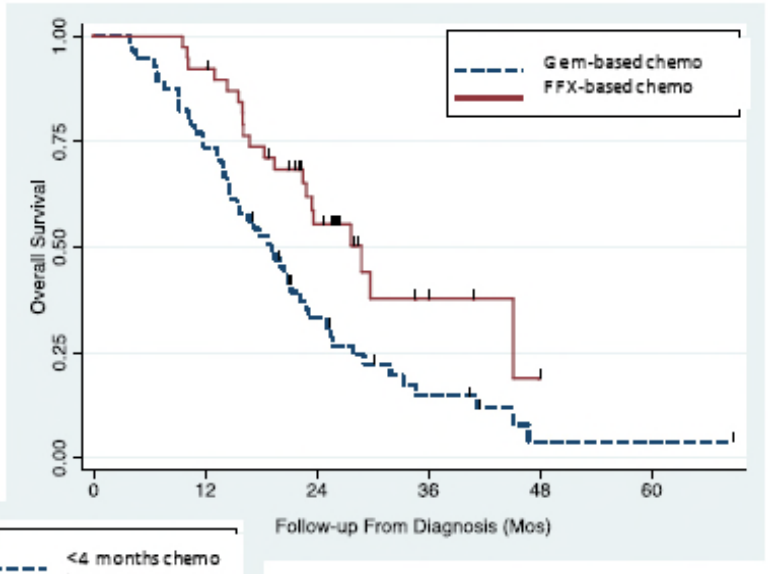


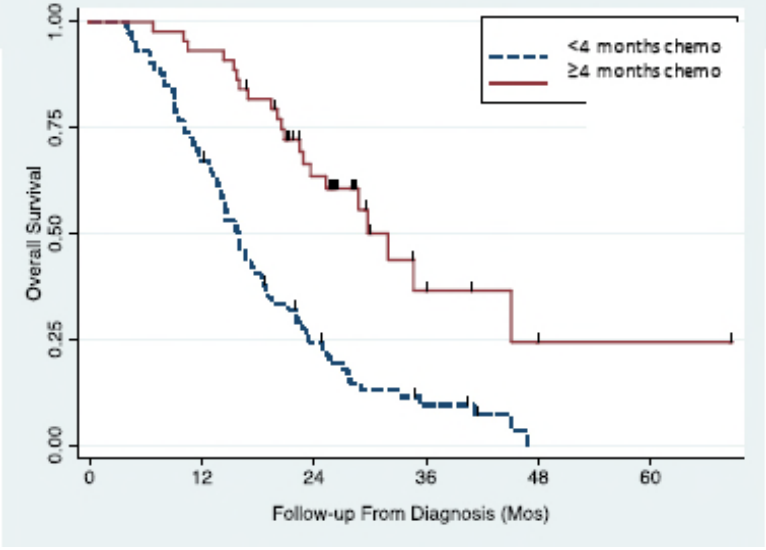
- Median OS from SBRT = 14.5 mos (95% CI: 12.2 – 18.6)

Courtesy by Dr. Rosati and Herman, ASTRO 2017

Multi-Agent Chemo and SBRT







Courtesy by Dr. Rosati and Herman, ASTRO 2017

Table 1 Recently Completed and Current Clinical Trials Evaluating the Role of SBRT in Pancreatic Cancer

Clinical Trial Identifier	Phase	Regimen	Disease Stage	Location	Date Opened	Status	Primary Outcome
NCT01992705		FOLFIRINOX → SBRT (6 Gy × 5)	BRPC	University of Maryland	March 2014	Recruiting	Downstaging to resectability
NCT02780648		SBRT (5–6.6 Gy × 5)	BRPC, LAPC, and recurrent	Indiana University	May 2016	Recruiting	Toxicity
NCT01342354	I	SBRT (3 fx)	LAPC, unresected, and recurrent	University of Chicago	April 2009	Recruiting	Toxicity
NCT01446458	I	mFFX → SBRT (12 Gy × 3)	Resectable or BRPC	Emory University	November 2011	Completed	Toxicity
NCT01872377	I	SBRT boost (6-10 Gy × 3)	LAPC	Ottawa Hospital Research Institute	July 2013	Recruiting	Toxicity
NCT01918644	I	SBRT + Cap	Resectable	University of Wisconsin, Madison	August 2013	Recruiting	Toxicity
NCT02454140	I	SBRT dose escalation (8-12 Gy × 5)	LAPC, medically inoperable	University of California, San Diego	June 2014	Recruiting	Toxicity
NCT02208024	I	SBRT (6.6 Gy × 5)	Resectable	University of Cincinnati	August 2014	Recruiting	Toxicity
NCT02311361	I	MEDI4736 ± tremelimumab → SBRT dose escalation	LAPC	National Cancer Institute	November 2014	Recruiting	Toxicity and feasibility
NCT02308722	I	SBRT dose escalation (6-7 Gy × 5)	BRPC	University of Oxford	April 2015	Recruiting	Toxicity
NCT02643498	I	Chemo → SBRT dose escalation (9-11 Gy × 3)	LAPC	Memorial Sloan Kettering	December 2015	Recruiting	Toxicity
NCT02716207	I	SBRT dose escalation (7-9.5 Gy × 5)	LAPC	Changhai Hospital	March 2016	Recruiting	Toxicity
NCT02873598	I	FFX or Gem/Nab-P → SBRT dose escalation (9-11 Gy × 3)	LAPC	University of Colorado, Denver	August 2016	Not Yet Open	Toxicity
NCT02868632	I	SBRT (6 Gy × 5) with MEDI4736, tremelimumab, or MEDI4736 + tremelimumab	LAPC	New York University	August 2016	Not Yet Open	Overall survival
NCT01304160	I/II	SBRT (6 Gy × 5) → Gem	LAPC	Centre hospitalier de l'Université de Montréal	September 2010	Completed	Toxicity
NCT01360593	II	Gem/Cap → SBRT (12 Gy × 3)	LAPC	University of Pittsburgh	July 2011	Active, Not Recruiting	Local progression-free survival
NCT01357525	II	SBRT (12 Gy × 3)	Resected	University of Pittsburgh	July 2011	Recruiting	Local progression-free survival
NCT01595321	II	SBRT + FFX ± GVAX vaccine	Resected	Johns Hopkins University	August 2012	Active, Not Recruiting	Toxicity
NCT01781728	II	Chemo → SBRT (5-6.6 Gy × 5)	LAPC, recurrent, and resected	Johns Hopkins University	January 2013	Recruiting	Toxicity
NCT01898741	II	SBRT (8 Gy × 3)	LAPC	UMC Utrecht	July 2013	Recruiting	Toxicity
NCT01959672	II	Gem/LV/5-FU ± oregovomab → SBRT + nelfinavir	LAPC	University of Nebraska	September 2013	Recruiting	Rate of progressive disease*

Table 1 (continued)

Clinical Trial Identifier	Phase	Regimen	Disease Stage	Location	Date Opened	Status	Primary Outcome
NCT02416609	II	LDR → Gem/Ox → SBRT (3 fx)	LAPC	University of Modena	January 2014	Recruiting	Progression-free survival
NCT02128100	II	FFX → SBRT (6.5 Gy × 5)	LAPC	James Graham Brown Cancer Center	May 2014	Recruiting	Toxicity
NCT02347618	II	SBRT	Resectable	University of Rochester	December 2014	Recruiting	Toxicity
NCT02241551	II	Gem/Nab-P vs mFFX + SBRT	BRPC	University of Pittsburgh	December 2014	Recruiting	Toxicity, pathologic complete response, and R0 resection
NCT02153450	II	Metformin	BRPC, LAPC	Case Comprehensive Cancer Center	May 2015	Recruiting	Toxicity
NCT02461836	II	Gem ± SBRT (5 Gy × 5)	Resected	Zhejiang University	August 2015	Recruiting	Disease-free survival
NCT02734680	II	IORT → 3 Gy × 15 Gem-CRT or SBRT → S-1	LAPC	Chinese Academy of Medical Sciences	February 2016	Recruiting	Overall survival
NCT02704143	II	S-1 + SBRT	LAPC	Changhai Hospital	March 2016	Recruiting	Overall survival
NCT02704156	II	SBRT (6.5–9 Gy × 5)	LAPC	Changhai Hospital	March 2016	Recruiting	Overall survival
NCT02745847	II	SBRT Reirradiation	Recurrent	Changhai Hospital	May 2016	Not Yet Open	Overall survival
NCT02723331	II	Gem/Nab-P → SBRT	Resectable, BRPC	University of Colorado, Denver	May 2016	Recruiting	R0 resection
NCT02648282	II	Cyclophosphamide, pembrolizumab + GVAX + SBRT	LAPC	Johns Hopkins University	July 2016	Recruiting	Distant metastasis-free survival
NCT01926197	III	mFFX ± SBRT	LAPC	Stanford University	August 2013	Recruiting	Progression-free survival

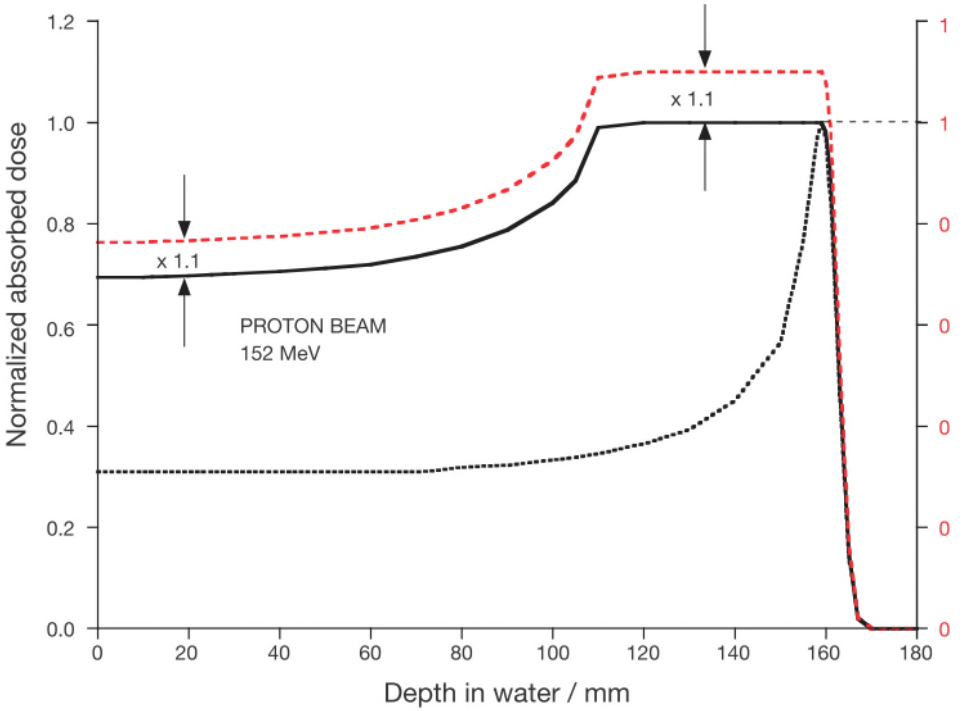
Abbreviations: SBRT, stereotactic body radiation therapy; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; mFFX, modified FOLFIRINOX; Cap, capecitabine; Gem, gemcitabine; LV, leucovorin; 5-FU, 5-fluorouracil; LDR, low-dose radiotherapy; Ox, oxaloplatin; Nab-P, nab-paclitaxel; IORT, intraoperative radiation therapy; CRT, chemoradiation.
*Progressive disease defined by RECIST.

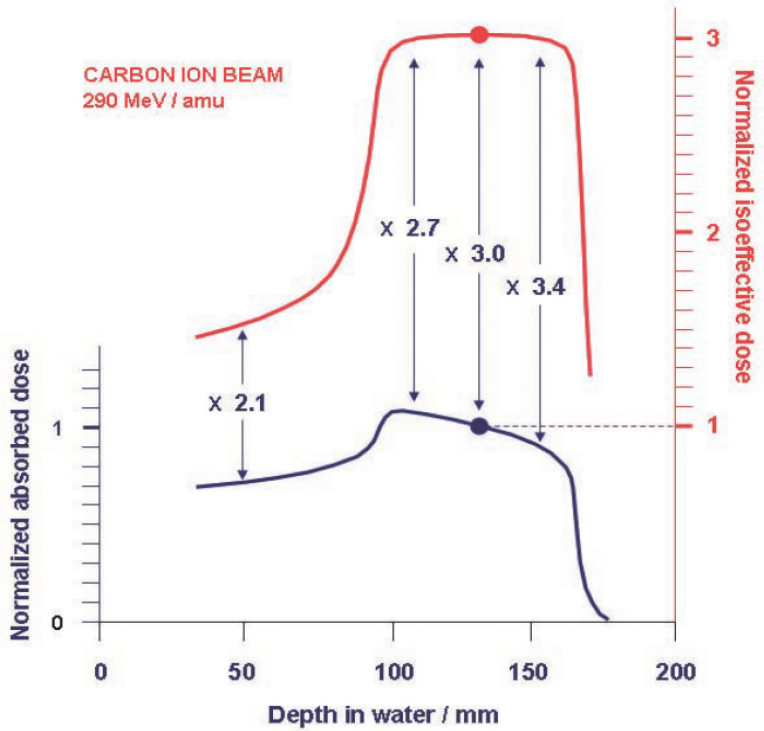
Completed and Current Clinical Trials Evaluating Role of SBRT in Pancreatic Cancer

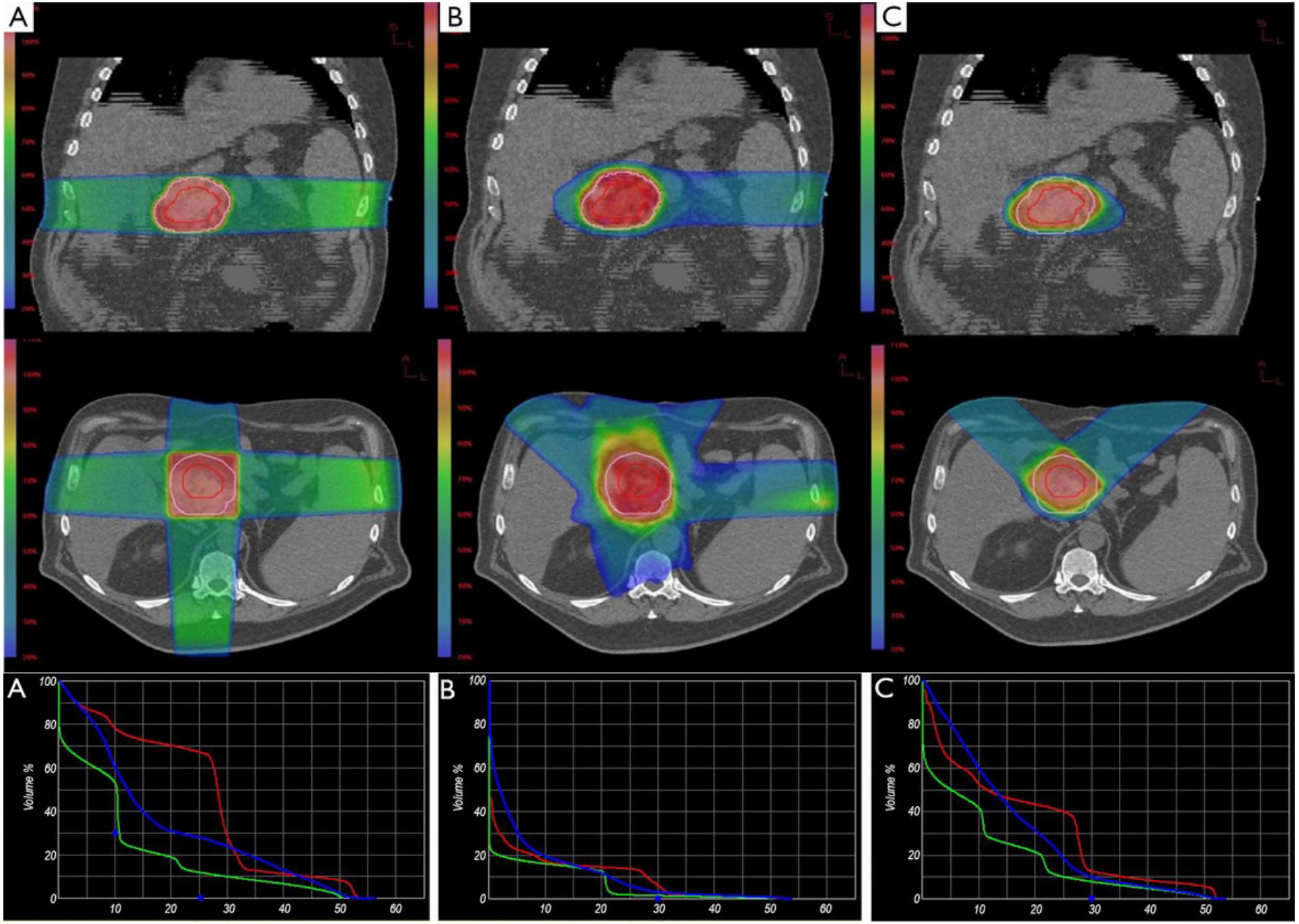
Rosati et al. Semin Radiat Oncol 2017;27:256

Charged Particle Therapy

- **Particle therapy** is a form of external beam radiotherapy using beams of energetic protons, neutrons, or positive ions for cancer treatment.
- **Proton therapy** is a type of particle therapy that uses a beam of protons to irradiate diseased tissue,
- Heavy-ion therapy is the use of particles more massive than protons or neutrons, such as carbon ions.


Normalized absorbed dose
1.2
1.0
0.8
0.6
0.4
0.2
0.0
x 1.1
x 1.1
PROTON BEAM
152 MeV
0
20
40
60
80
100
120
140
160
180
Depth in water / mm
1
1
0
0
0
0
0


CARBON ION BEAM
290 MeV / amu
x 2.7
x 3.0
x 3.4
x 2.1
Normalized absorbed dose
1
0
0
50
100
150
200
Depth in water / mm
3
2
1
Normalized isoeffective dose



Ling et al. J Gastrointest Oncol 2015;6:108

ChemoRadiation or Chemotherapy for Locally Advanced Pancreatic Cancer

	Year	#	Treatment	Dose	Survival	
					1yr	2yr
ECOG	2008	34	GEM+RT	50.4Gy/28Fx	50%	12%
		37	GEM	-	32%	4%
Ishii	2010	50	GEM	-	64%	14%
Sudo	2011	34	S-1+RT	50.4Gy/28Fx	71%	25%
Small	2011	28	GEM+BZ+RT	36Gy/15Fx	45%	17%
Schellenberg	2011	20	GEM+SBRT	25Gy/1Fx	50%	20%
NIRS	2016	48	GEM+CIRT	45.6–55.2 GyE/12Fx	78%	48%

Courtesy by Dr Tadashi Kamada

Novel RT for Pancreatic Cancer

	IMRT	SBRT	Proton	Carbon
Insufficient Dose → Dose Escalation	+	+++	++	++
Radiation-Induced Toxicity → Sparing Normal Tissue	++	++	+++	+++
Intrinsic Radioresistance → Enhanced Biologic Effects	-	++	-	+++
Frequent Distant Metastasis → Bystander Effects → Combined Systemic Agents	- ++	+ +	- ++	+ ++
Conflicting Clinical Evidences → Large Well-Designed Studies	+	++	+	-

Registered Clinical Trials

- **Clinicaltrial.gov (2018.3.22)**
  - 5 studies found for: pancreas| cancer| radiotherapy| intensity| modulated
  - 47 studies found for: pancreas| cancer| radiotherapy| stereotactic
  - 8 studies found for: pancreas| cancer| radiotherapy| proton
  - 2 studies found for: pancreas| cancer| radiotherapy| carbon

Conclusion

- Novel techniques such as IMRT, IGRT, SBRT, or CPT are becoming routine for pancreatic cancer and may lead to better LC with less toxicity.
- Nonetheless, further study to assess outcomes with these new technologies is warranted to ensure appropriate utilization and to standardize the quality of care.


Thank you !