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Stereotactic body radiation therapy for locally advanced pancreatic cancer (LAPC)

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Background

- CA pancreas is one of the most devastating solid tumours and is the 6th commonest cause of cancer mortality in Hong Kong
- Surgery is the standard of care for resectable disease while radical concurrent chemoradiotherapy or chemotherapy alone are indicated for unresectable diseases (LAPC)
- However radical chemoradiotherapy is also associated with high rate of G3/4 toxicities, with a median survival of 5-15 months
- After even after radical resection +/- adjuvant treatment, about 30% died of local disease with minimal or no metastases

Chemoradiotherapy

- 3-dimensional (conformal RT or IMRT) with standard fractionation scheme of 1.8-2 Gy fractions to 50.4-54Gy over 5 to 6 weeks
- Concurrent with 5-FU, capecitabine, TS-1 or gemcitabine
- Mainly provide local control, palliation and occasional downsizing/downstaging tumours leading to improved resectability
- Modest impact on overall prognosis

Author	Year	RT tech.	RT	Chemo	n	MST (mo)	1yOS	2yOS	≥G3 GI toxicity
Loehrer	2011	3DCRT	-	Gem alone	37	9.2	32%	5%	31%
			50.4Gy/ 28F	Gem	34	11.0	50%	12%	68%
Ikeda	2013	3DCRT	50.4Gy/ 28F	TS-1	60	16.2	72%	-	10%
Hammel	2016	3DCRT	-	NAC+Gem/ER	136	16.4	-	-	1%
			54Gy/30F	NAC+Gem	133	15.2	-	-	11%
Ben-Josef	2012	IMRT	50-60Gy/25F	Gem	50	14.8	-	30%	22%
Terashima	2012	Proton	67.5Gy/ 25F	Gem	40	-	79%	-	32%
Shinoto	2016	C-ion RT	45.6-55.2Gy/ 12F	Gem	42	23.9	79%	48%	5%
Kamada	2017	C-ion RT	55.2Gy/ 12	Gem and/or TS-1	34	NA	85%	65%	7%

Stereotactic body radiation therapy

- Use of a 3-dimensional stereotactic system to track the position of the patient and the tumour(s) before and during treatment, thus allowing a high-dose radiation in 1-6 fractions to the tumour and regional lymphatics and minimal to low radiation dose to the surrounding structures

Restriction of tumour motion by respiratory control technique

- Active breathing control (ABC)
- Gating technique
- Abdominal compression (more commonly used for HCC)

Active breathing control (ABC)

- The ABC apparatus is a modified spirometer consisting of two pairs of flow monitors and scissor valves to control inspiration and expiration, respectively
- The operator activates ABC at a predefined lung volume by closing both valves to immobilise the breathing motion for 15 to 20 seconds
- Pre-treatment breath-hold training is required
- Simultaneously the linac radiation beam is switched on until towards the end of the tolerance of breath hold of the patient
- Patient is allowed to breath freely afterwards after each breath hold
- Each patient needs to take breath holds for an average of 10-15 times in each fraction of SBRT
- The total duration for each fraction of SBRT is about 15-20 minutes

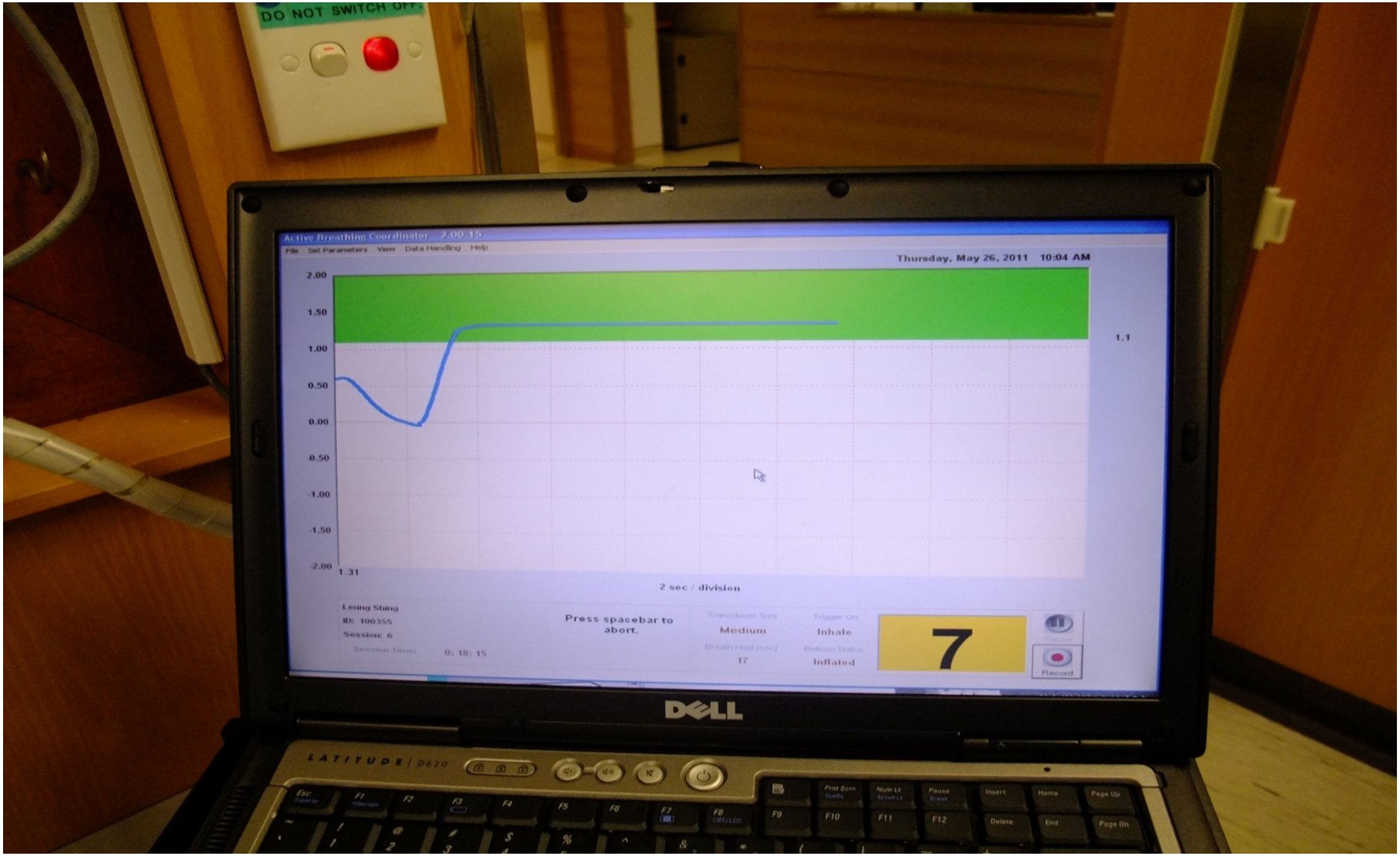
Active breathing control (ABC)

- Breath hold at maximal inspiration for thoracic SBRT (spares the lungs from excessive irradiation)
- Breath hold at maximal expiration for abdominal SBRT (spares the liver from excessive irradiation and more comfortable to patients with distending tumours)

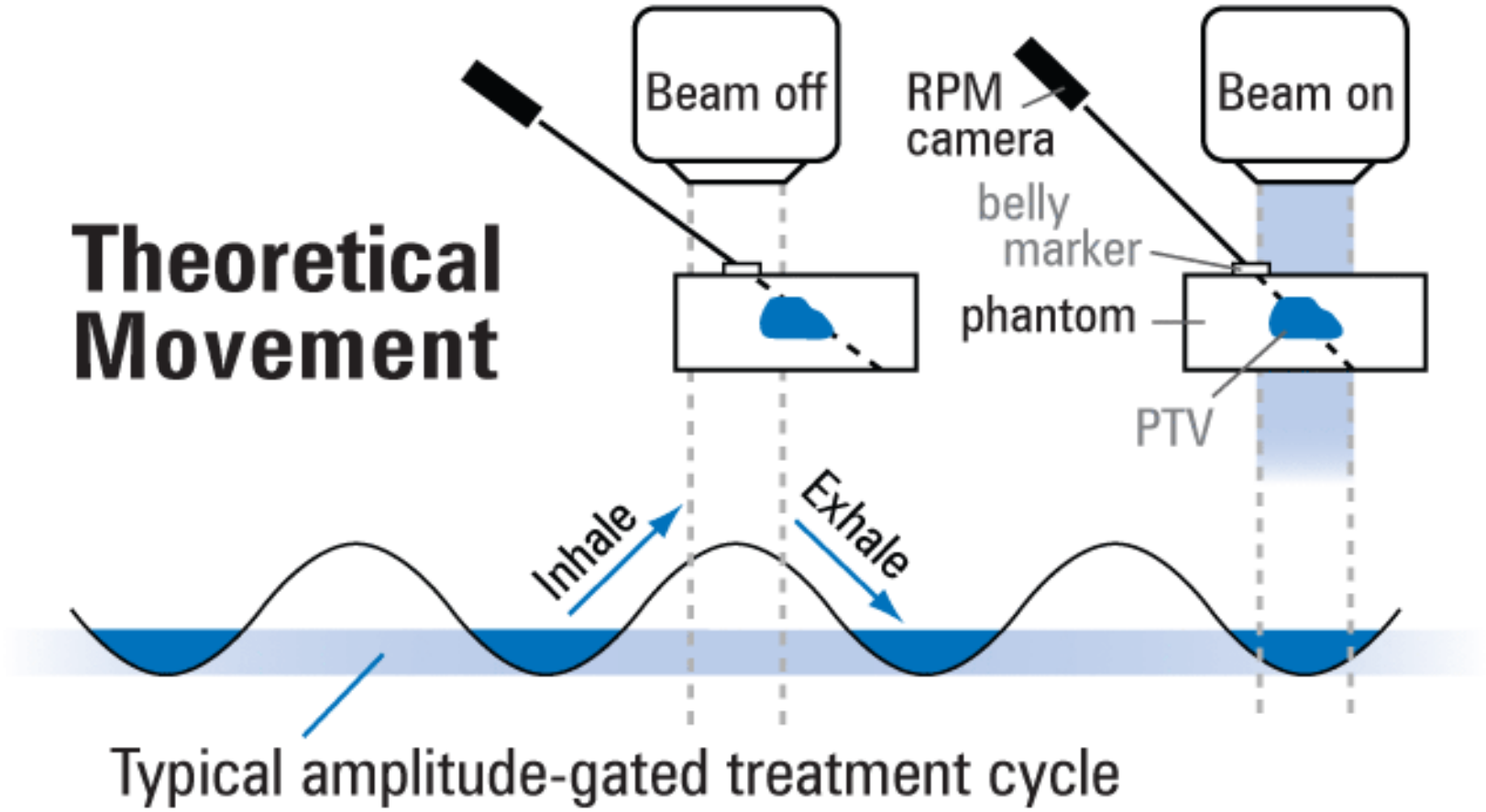
Active Breathing Control technique

ABC technique

ABC technique for a patient with CA lung (breath-hold at maximal inspiration)



Gating technique



Source:Standardimaging.com

Gating technique

- Radiation therapy delivered during certain phases of the respiratory cycles, especially during end-expiratory phase for liver tumours

Abdominal compression

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 3, pp. 938–946, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.003

PHYSICS CONTRIBUTION

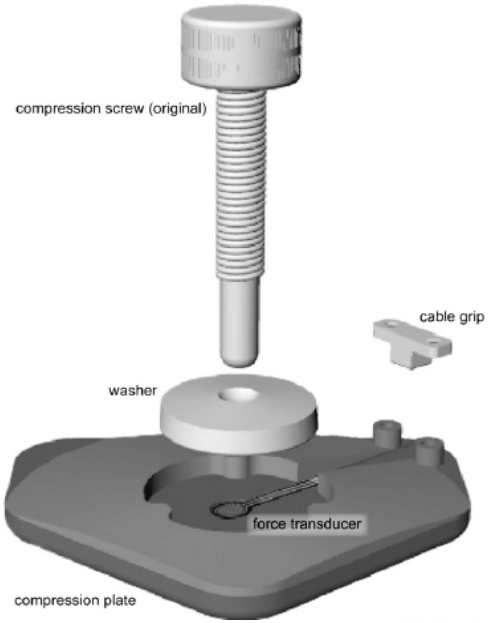
INTERFRACTION LIVER SHAPE VARIABILITY AND IMPACT ON GTV POSITION DURING LIVER STEREOTACTIC RADIOTHERAPY USING ABDOMINAL COMPRESSION

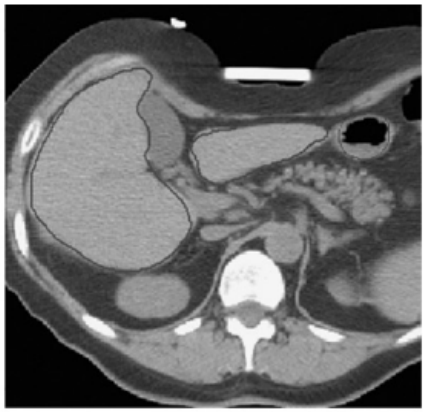
CYNTHIA L. ECCLES, B.SC., LAURA A. DAWSON, M.D., JOANNE L. MOSELEY, PH.D., AND KRISTY K. BROCK, PH.D.

Radiation Medicine Program, Princess Margaret Hospital, and University of Toronto, Toronto, Ontario, Canada

IJROBP 2011;80:938-46

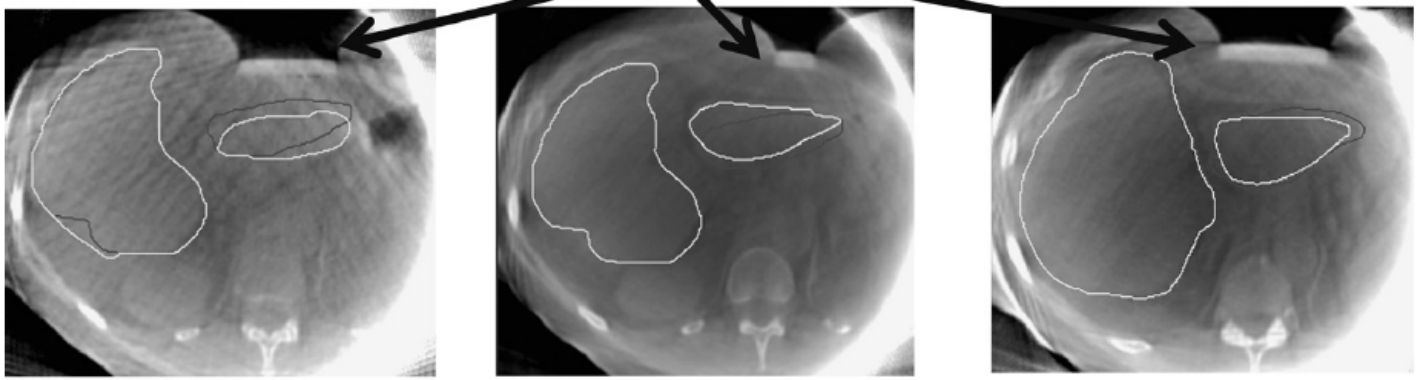
Abdominal compression





Planning CT: liver outlined in black

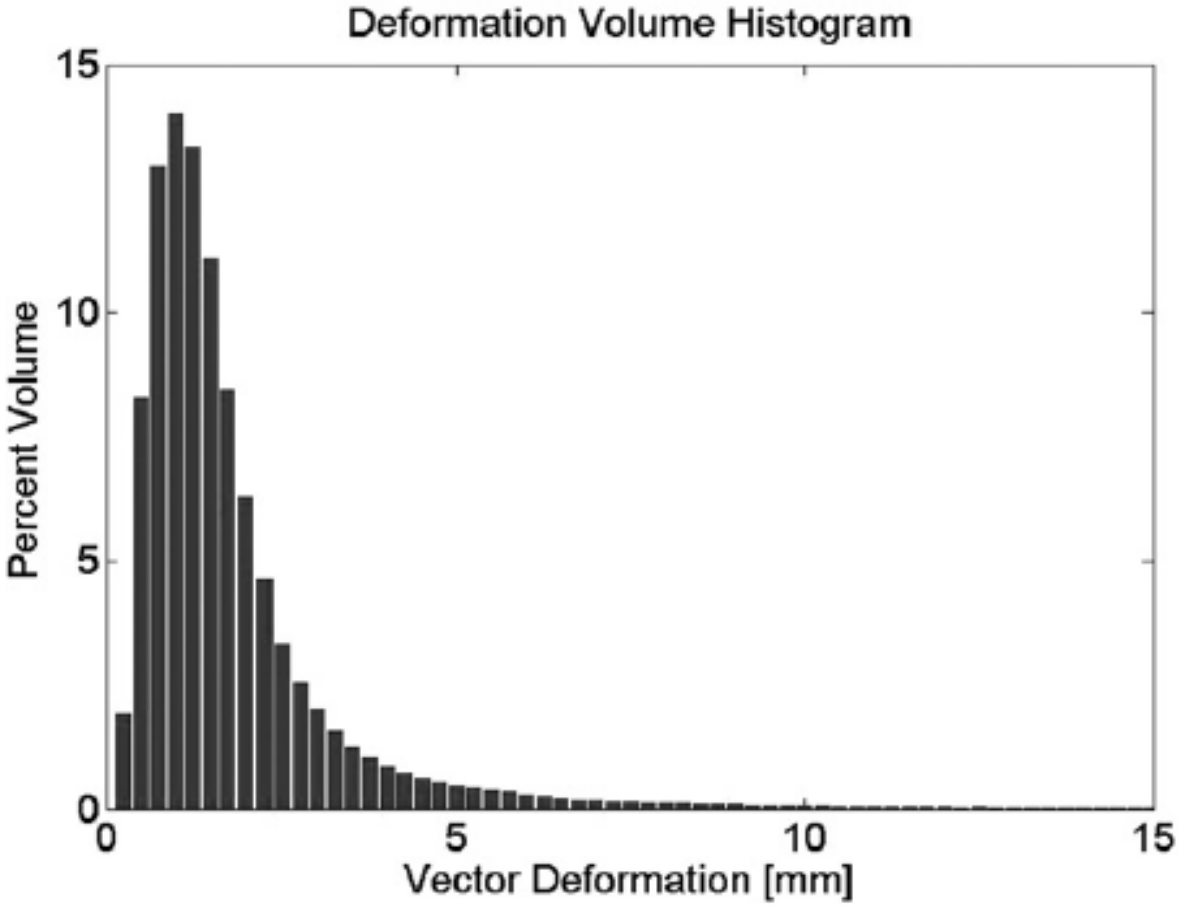
Abdominal compression plate



CBCT from fractions 1, 5, 6 with liver from planning CT (dark contour), and liver from CBCT of each fraction (white contour).

IJROBP 2008;71:907-15; IJROBP 2011;80:938-46

Liver deformation by abdominal compression



Liver can be deformed up to 15mm and 13% in volume by abdominal compression

IJROBP 2011;80:938-46

Fiducial markers

- Important as radiographic markers to allow image-guided radiotherapy (IGRT)
- Accurate positional verification can be achieved to allow high-dose radiation to the tumours sparing surrounding organs at risk
- Fiducial markers (usually 2-4) can be either percutaneously or endoscopically via ultrasonography guidance
- They are usually placed at the periphery of the tumour separated by ample distance and angulation for IGRT

Fiducial markers

Gastrointest Endosc. 2012 November ; 76(5): 962–971. doi:10.1016/j.gie.2012.07.006.

Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy

Mouen A. Khashab, MD[*,1], **Katherine J. Kim, MHS**[*,1], **Erik J. Tryggestad, PhD**[2], **Aaron T. Wild, BA**[2], **Teboh Roland, PhD**[2], **Vikesh K. Singh, MD, MSc**[1], **Anne Marie Lennon, MD, PhD**[1], **Eun Ji Shin, MD**[1], **Mark A. Ziegler, BS**[2], **Reem Z. Sharaiha, MD, MSc**[1], **Marcia Irene Canto, MD, MHS**[1], and **Joseph M. Herman, MD, MSc**[2]

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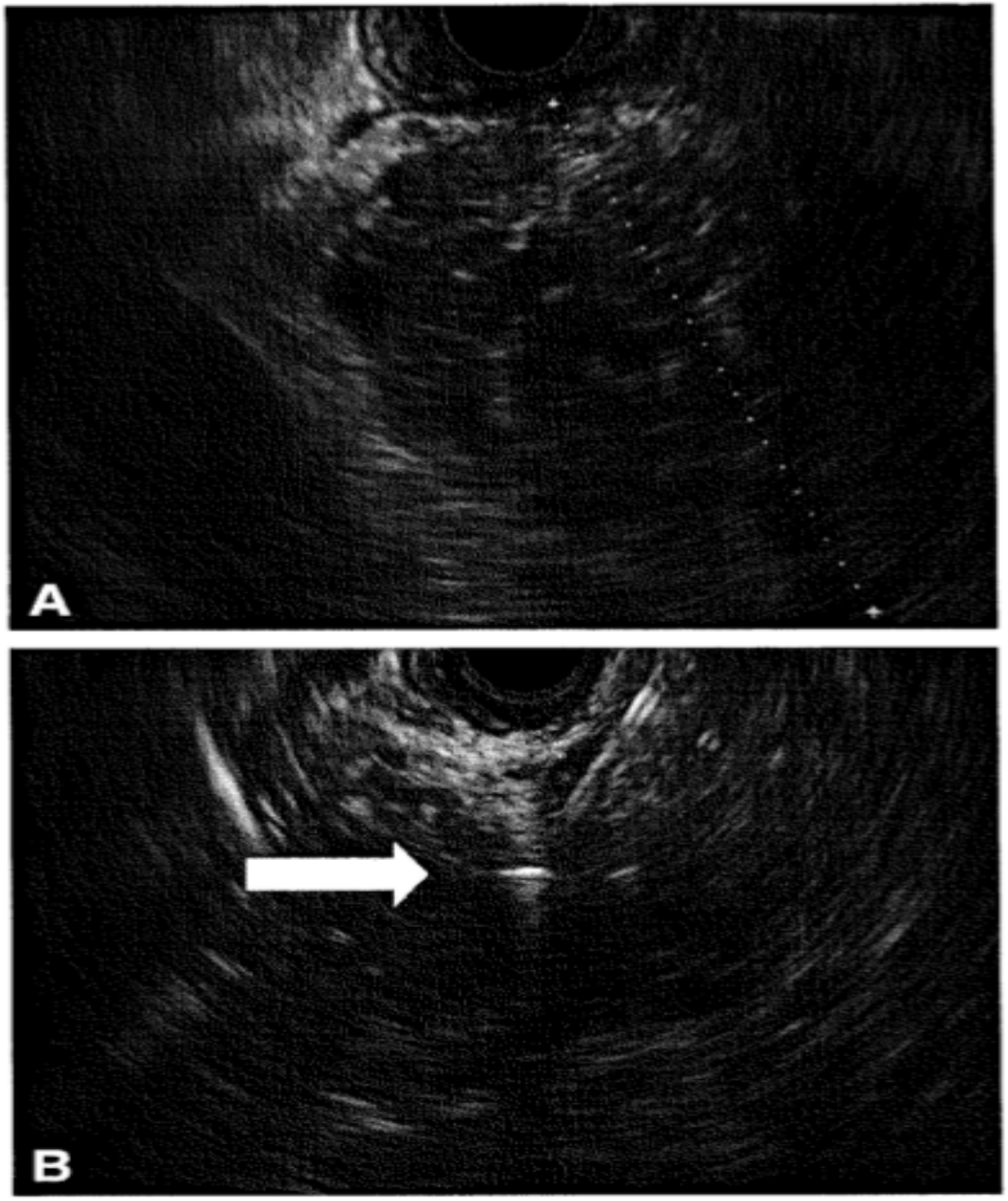
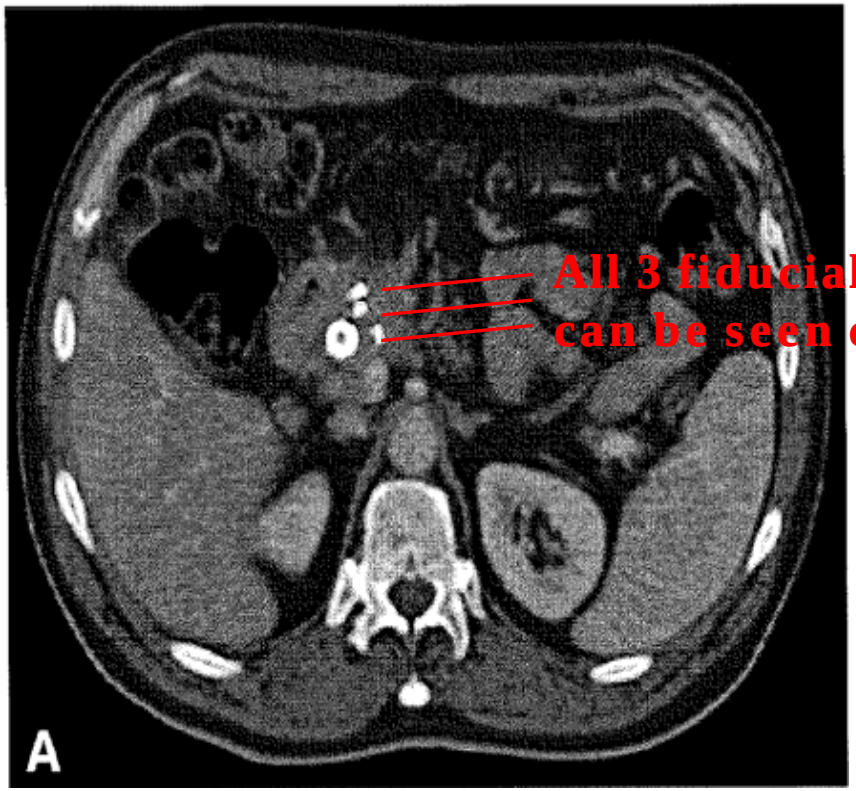
Mouen et al. Gastrointest Endosc 2012

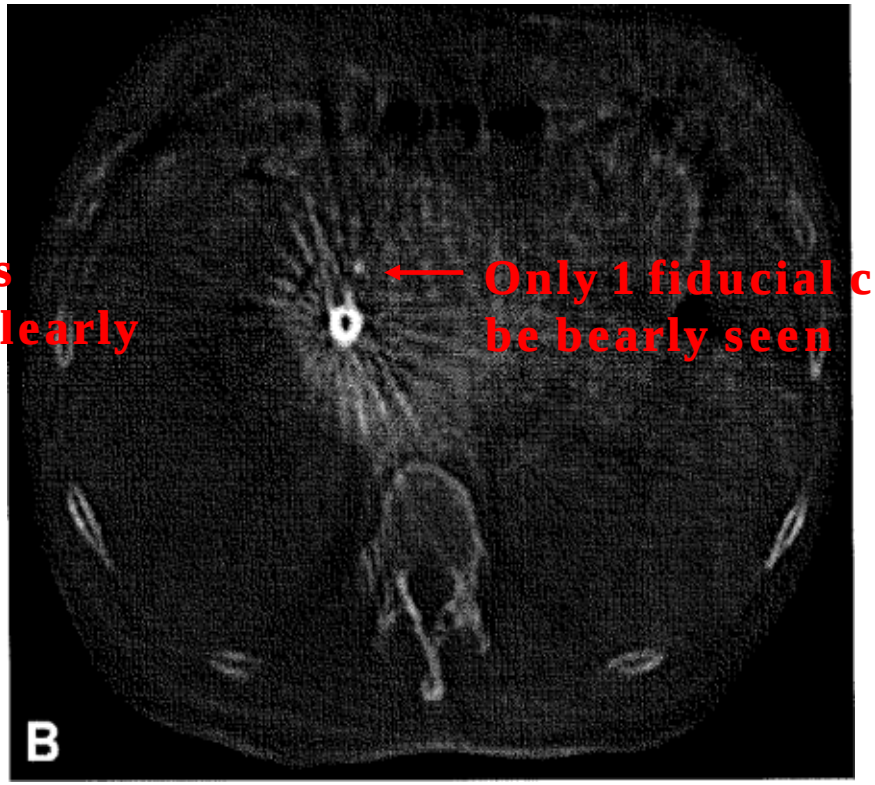


Placement of fiducial markers under EUS

Fiducial markers

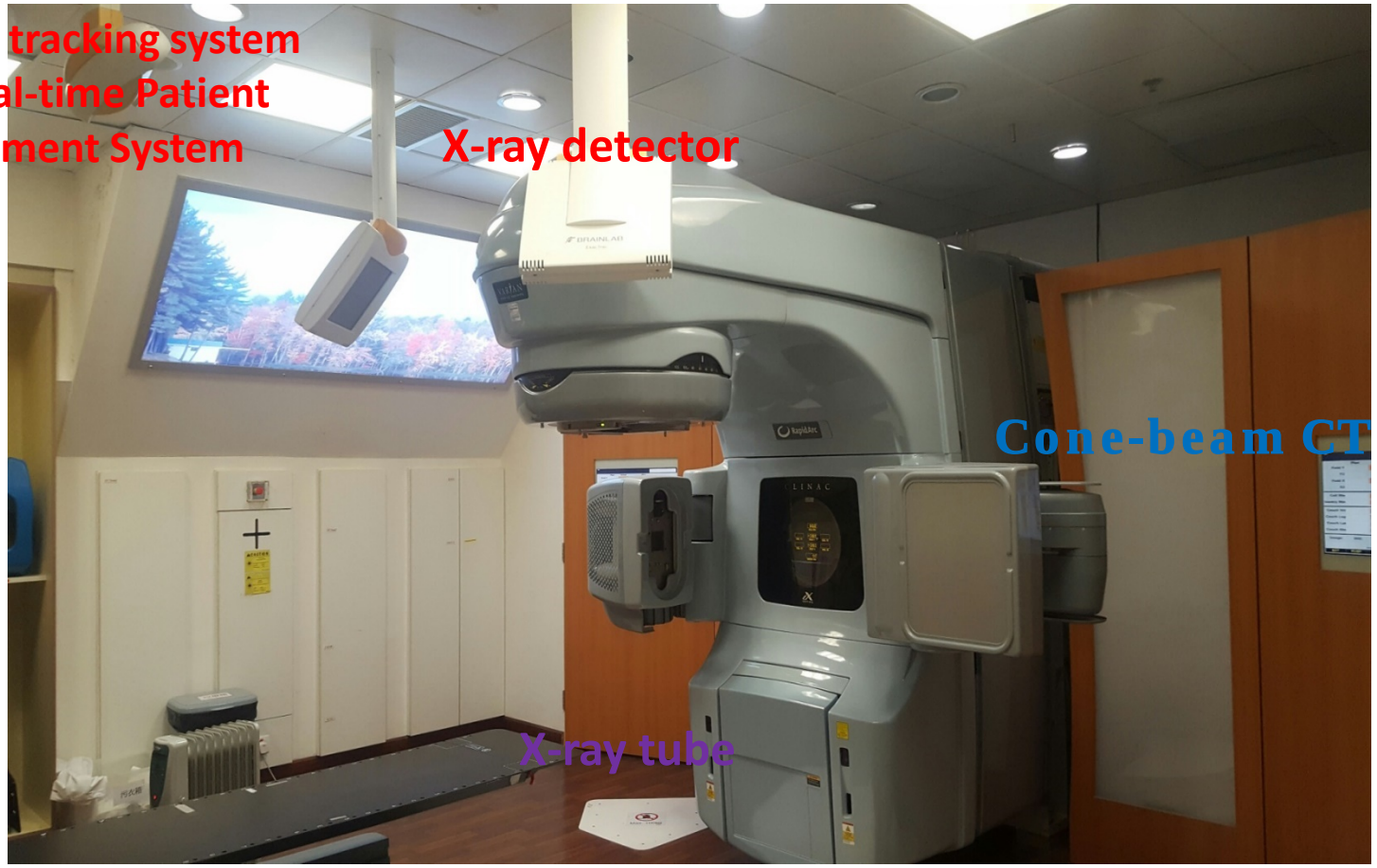


Good positional verification of the fiducials



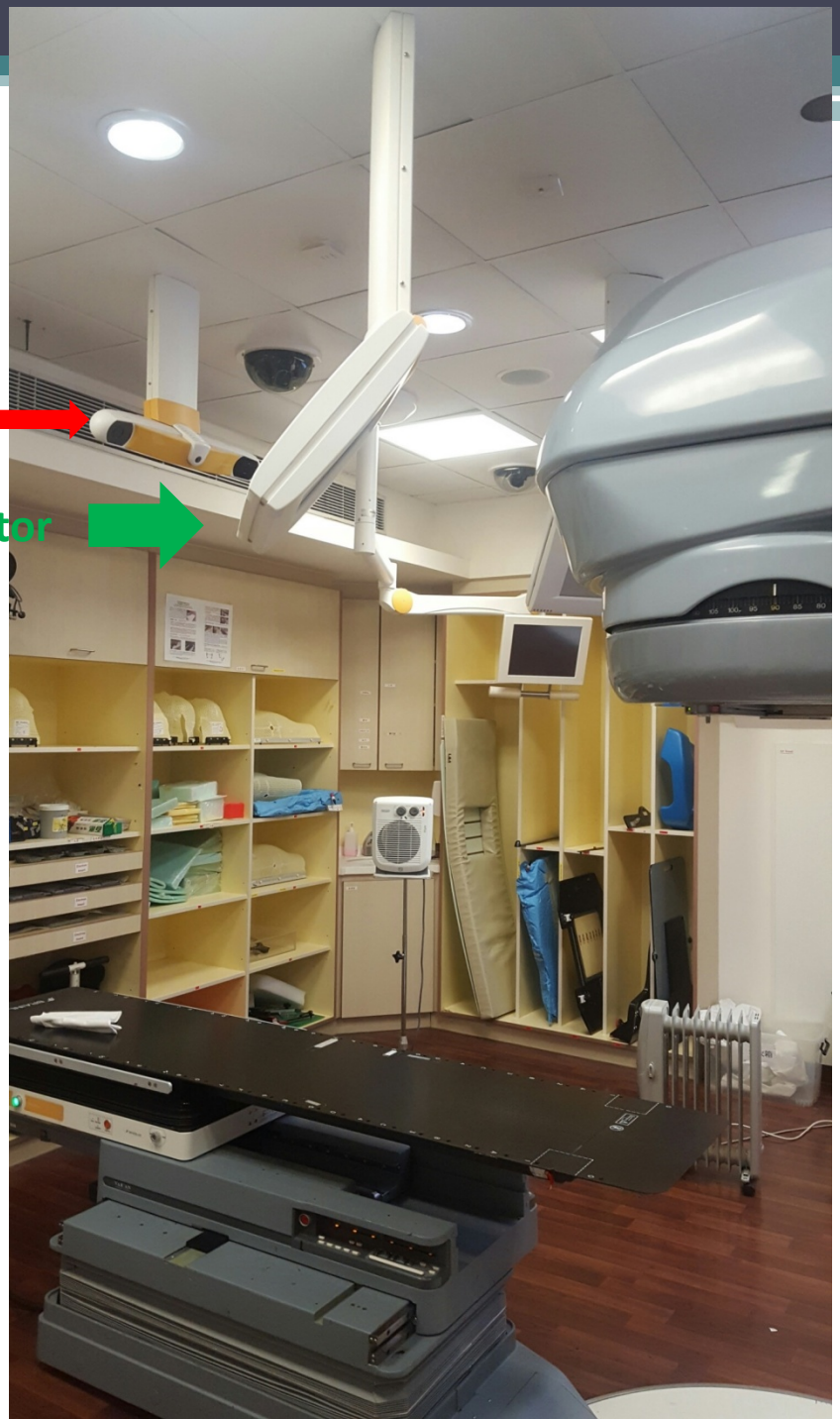
Poor positional verification of the fiducials

Our linear accelerator with ExacTrac (BrainLab) Image-guided Radiotherapy System



Infrared detector

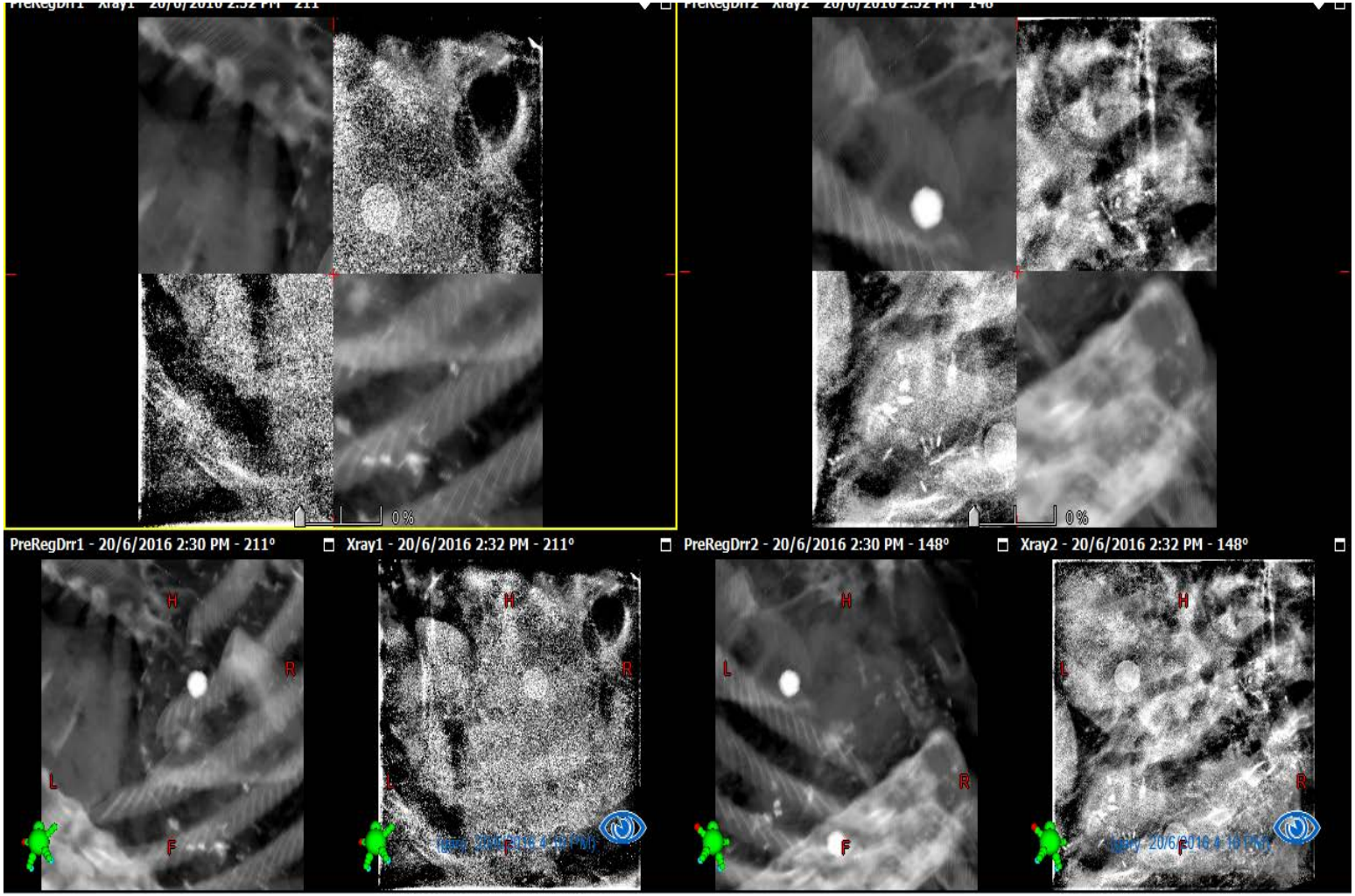
X-ray detector



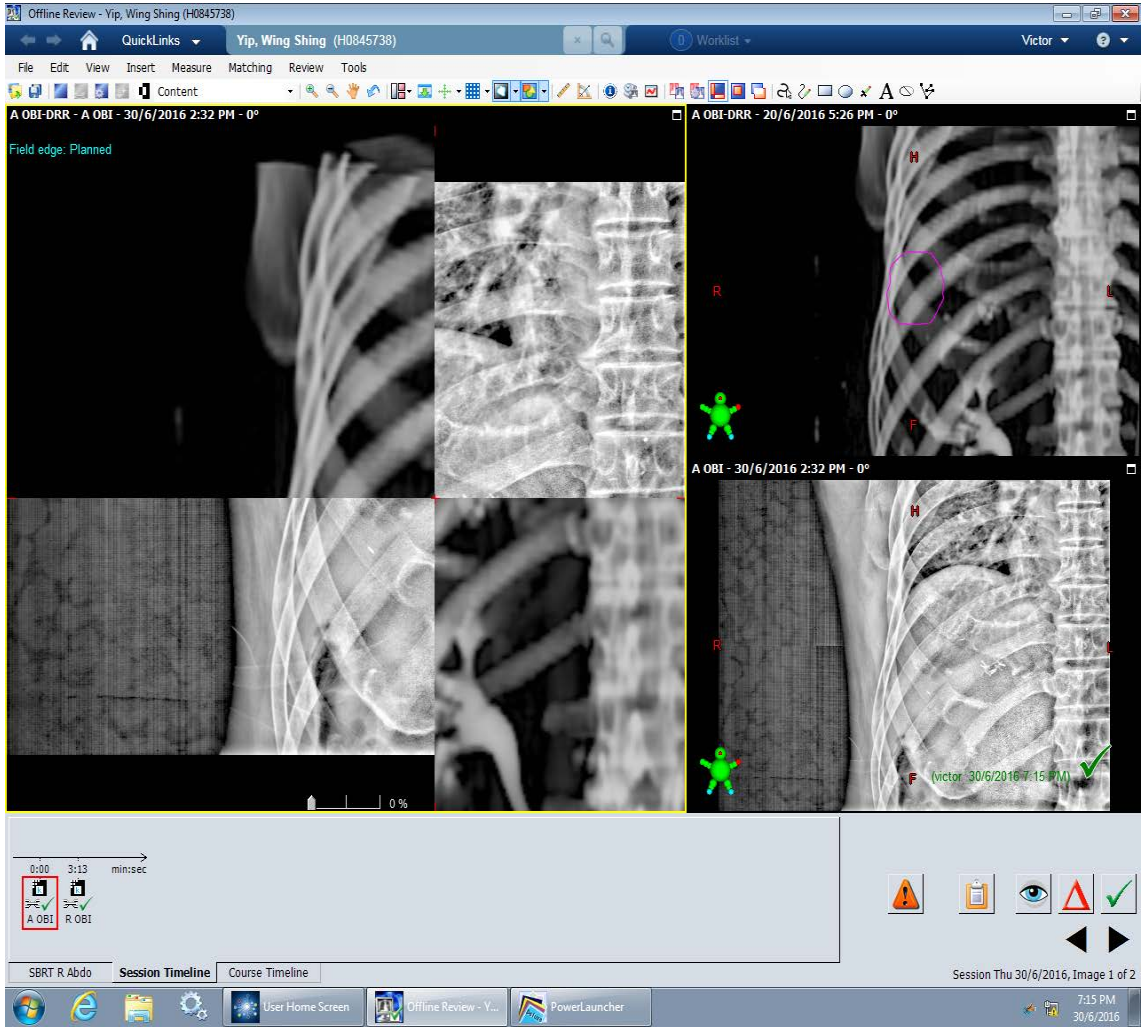
Positional verification before treatment

- Exactrac patient monitoring (BrainLab AG, Germany)
- On-board imaging
- Cone-beam CT scan

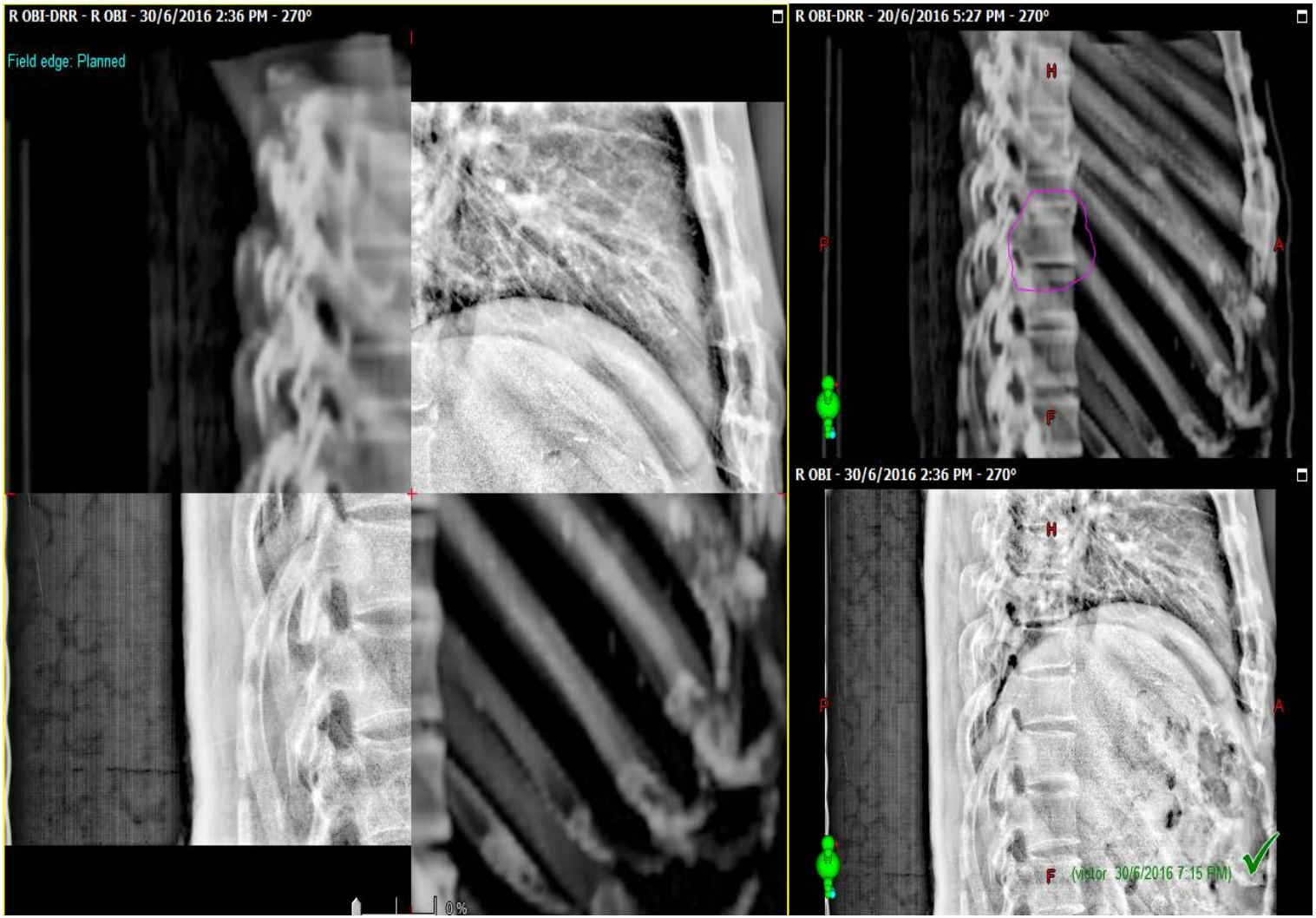
ExacTrac positional verification



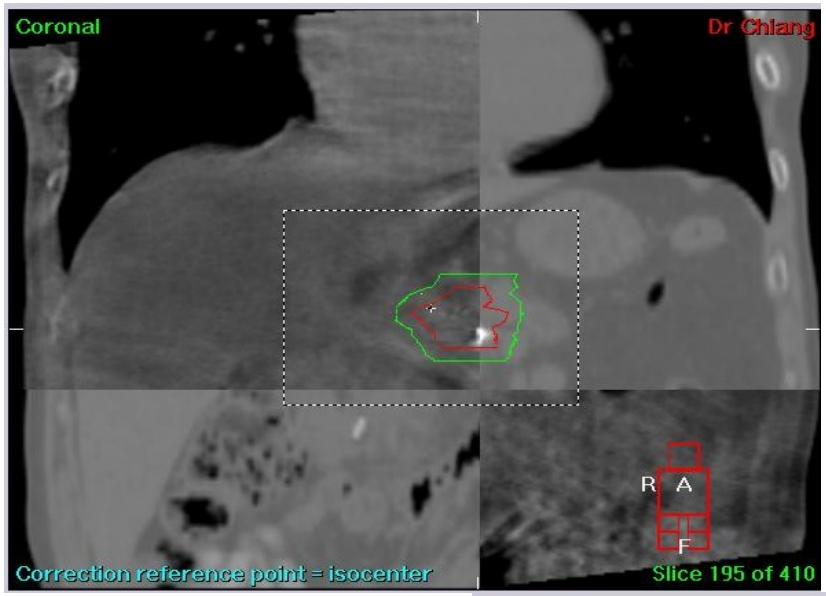
On-board imaging – AP position

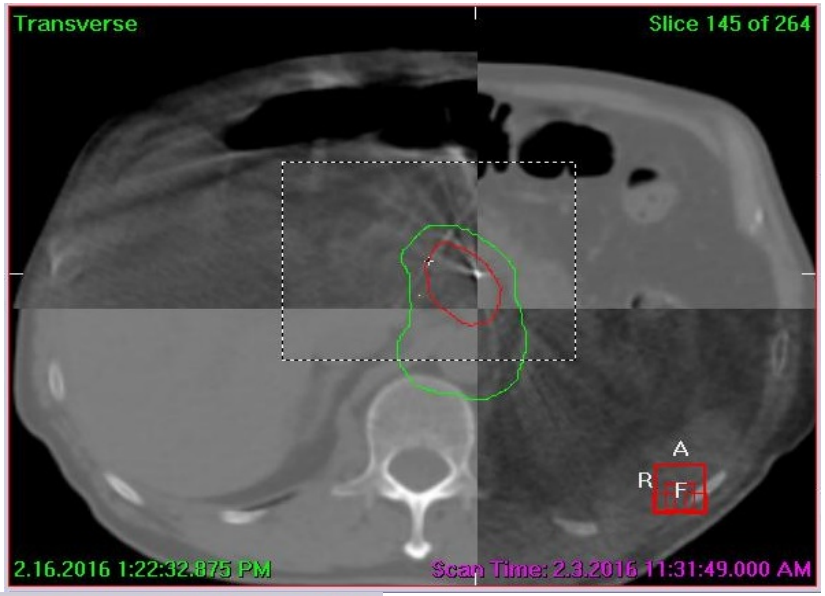


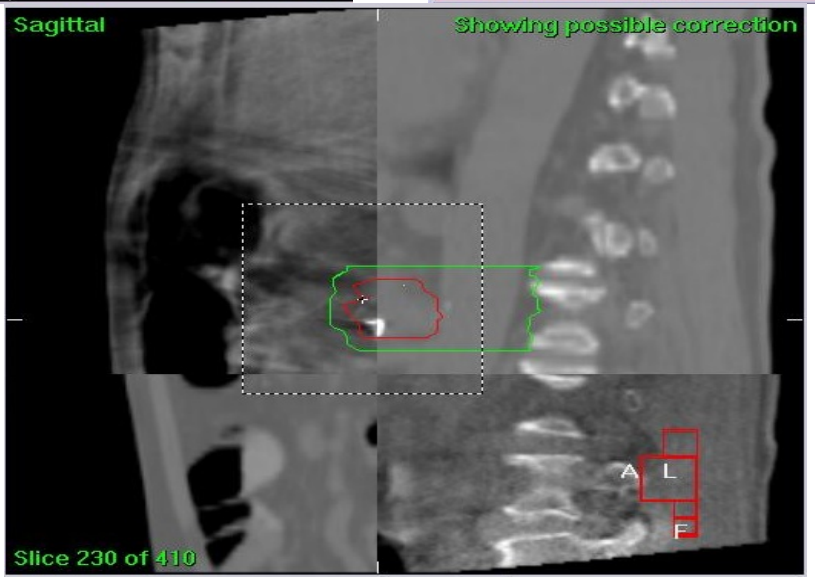
On-board imaging – Lateral position



Cone-beam CT imaging





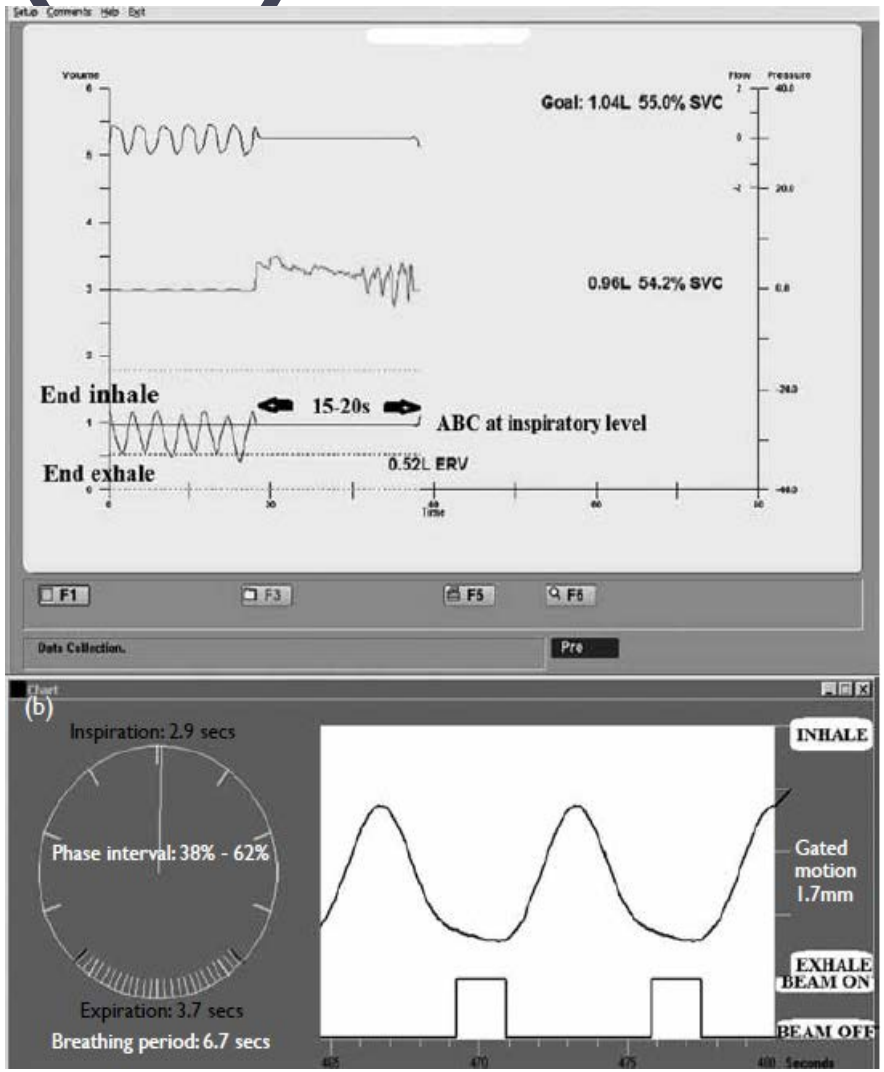


Courtesy of Dr. CL Chiang

Tracking of respiratory cycles during SBRT

- Achieved by Real-time Patient Management Systems (RPM) (Varian Medical Systems, Palo Alto, CA, USA)
- Consists of an infrared reflective block and an infrared tracking camera. The reflective block is placed on the anterior abdominal skin surface
- The infrared camera then tracks motion of the reflective block
- The up-and-down breathing movements of the abdominal wall shown by the motion of the reflective blocks will reflect the whole respiratory phase

Real-time Patient Management Systems (RPM)



Tsang et al. Hong Kong Med J 2014;20:529-36

GTV, CTV, ITV and PTV

- Gross tumour volume (GTV)
  - The grossly demonstrable lesion on CT and MRI
  - MRI with contrast for better delineation of target lesion
- Clincal target volume (CTV)
  - The volume of the lesion which takes into account of occult microscopic spread of the disease
  - Usually GTV=CTV in SBRT, ie no margin added from GTV to CTV
  - Occasionally may be 2mm margin around GTV is added for individual cases

GTV, CTV, ITV and PTV

- Internal target volume (ITV)
  - The volume of the lesion which takes the physiological motion of the patient/tumour into account
  - No margin if treated with ABC technique
  - If gating technique is used, ITV will be determined from the 4D CT images which encompass the whole respiratory cycle
- Planning target volume (PTV)
  - The treated volume of the lesion which takes the setup error into account
  - Usually 2-3mm margin around ITV

Dose fractionation

- 5.5Gy to 9Gy per fraction for 5 fractions over 1-2 weeks

SBRT results

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, MSc[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]

Herman et al. Cancer 2015

Gem + SBRT (33Gy/5Fr) + GEM

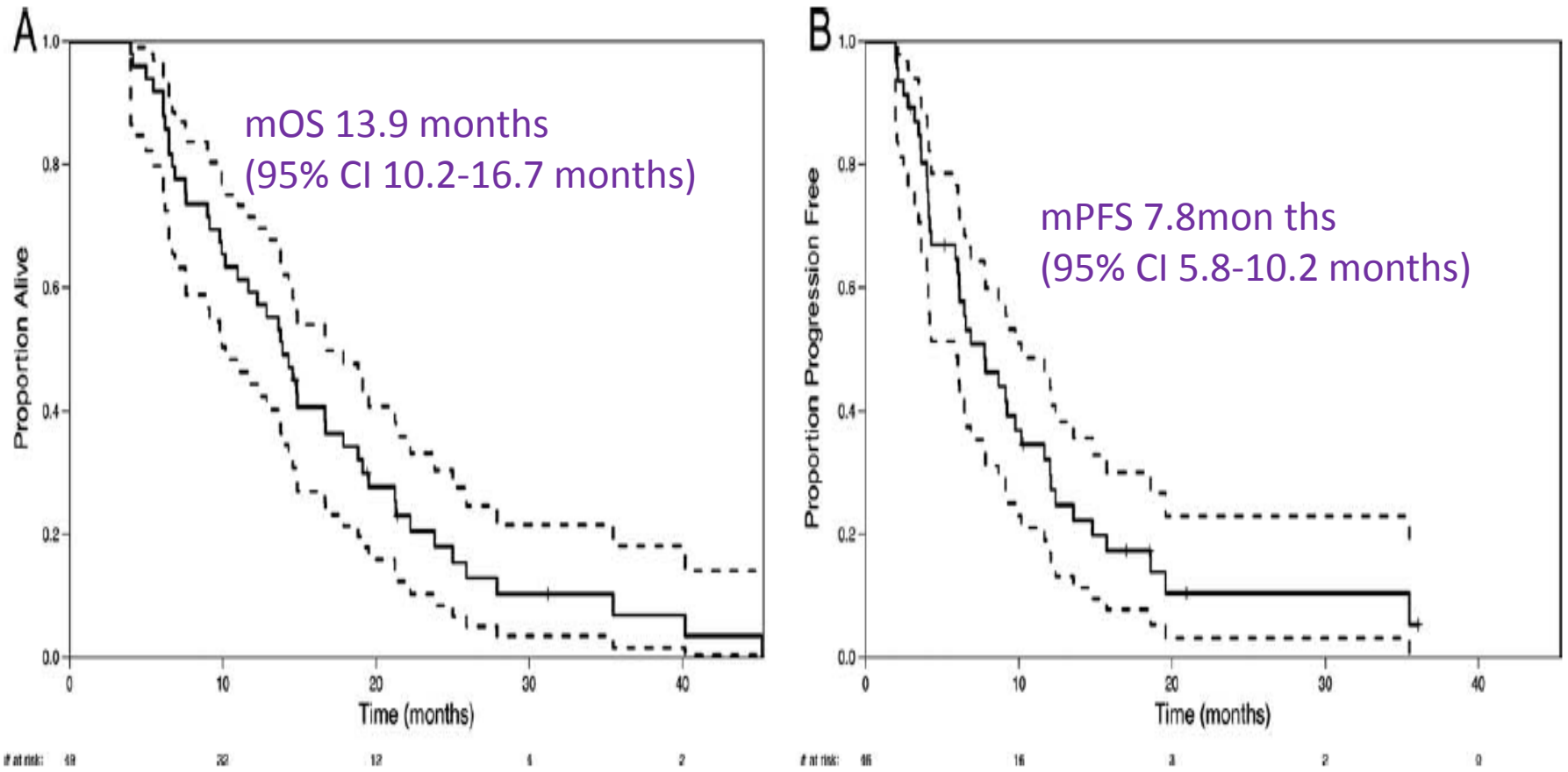


Figure 2. Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.

Herman et al. Cancer 2015

TABLE 3. Acute and Late GI Toxicities Within 90 Days of SBRT Broken Down by Time Frame, Type, and Severity[a]

Category	Total Grade ≥2 (%)	Total Grade ≥3 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Acute toxicity (*n*=49)						
Nonhematologic						
Enteritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcer	1 (2.0)	1 (2.0)	0 (0)	0 (0)	1 (2.0)	0 (0)
Other GI toxicities						
ALT/AST elevation	7 (14.3)	5 (10.2)	2 (4.1)	5 (10.2)	0 (0)	0 (0)
Abdominal pain	12 (24.5)	0 (0)	12 (24.5)	0 (0)	0 (0)	0 (0)
Anorexia	13 (26.5)	0 (0)	13 (26.5)	0 (0)	0 (0)	0 (0)
Constipation	3 (6.1)	0 (0)	3 (6.1)	0 (0)	0 (0)	0 (0)
Dehydration	2 (4.1)	1 (2.0)	1 (2.0)	0 (0)	0 (0)	1 (2.0)[b]
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspepsia/heartburn	4 (8.2)	0 (0)	4 (8.2)	0 (0)	0 (0)	0 (0)
Fatigue	13 (26.5)	0 (0)	13 (26.5)	0 (0)	0 (0)	0 (0)
Nausea	6 (12.2)	0 (0)	6 (12.2)	0 (0)	0 (0)	0 (0)
Weight loss	2 (4.1)	0 (0)	2 (4.1)	0 (0)	0 (0)	0 (0)
Other	1 (2.0)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (2.0)[c]
Hematologic						
Anemia	14 (28.6)	0 (0)	14 (28.6)	0 (0)	0 (0)	0 (0)
Lymphopenia	18 (36.8)	4 (8.2)	14 (28.6)	4 (8.2)	0 (0)	0 (0)
Neutropenia	3 (6.1)	1 (2.0)	2 (4.1)	1 (2.0)	0 (0)	0 (0)
Thrombocytopenia	6 (12.2)	1 (2.0)	5 (10.2)	1 (2.0)	0 (0)	0 (0)
Late toxicity (*n*=47)						
Enteritis	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Fistula	1 (2.1)	1 (2.1)	0 (0)	0 (0)	1 (2.1)	0 (0)
Gastritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcer	3 (6.4)	3 (6.4)	0 (0)	3 (6.4)	0 (0)	0 (0)
Other						
Pain	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Anorexia	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Other	2 (4.2)	2 (4.2)	0 (0)	1 (2.1)[d]	0 (0)	1 (2.1)[e]

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TABLE 4. Overall Survival[a]

	N	Median OS (95% CI), Months	1-Year OS	2-Year OS	HR	95% CI	*P*
All subjects	49	13.9 (10.2-16.7)	59%	18%			
Age ≤65 y	16	18.8 (13.9-21.3)	88%	14%	1	–	.343
Age >65 y	33	11.0 (7.5-14.8)	45%	20%	1.4	0.72- 2.54	
Male	31	14.6 (9.1-18.8)	58%	12%	1	–	.845
Female	18	13.7 (9.0-19.5)	61%	28%	0.94	0.50-1.74	
ECOG PS 0	21	16.7 (13.6-22.2)	81%	28%	1	–	.075
ECOG PS 1	28	9.1 (6.4-14.8)	43%	9%	1.72	0.93-3.15	
Tumor in head	41	14.3 (10.1-19.1)	61%	20%	1	–	.233
Tumor in body/tail	8	10.4 (3.9-16.7)	50%	12%	1.65	0.71-3.77	
Baseline CA 19-9 <90 U/μL	18	16.4 (13.9-19.5)	78%	20%	1	–	.129
Baseline CA 19-9 ≥90 U/μL	27	11.7 (6.4-21.2)	48%	20%	1.66	0.85-3.22	
Post-SBRT CA 19-9 <90 U/μL	26	14.8 (12.2-19.5)	73%	21%	1	–	.071
Post-SBRT CA 19-9 ≥90 U/μL	20	10.2 (6.1-16.7)	45%	12%	1.76	0.94-3.30	
No Pre-SBRT GEM[b]	5	9.0 (4.9-infinity)	40%	20%	1	–	.466
Received Pre-SBRT GEM	44	14.6 (10.1-17.9)	61%	17%	0.70	0.27-1.82	
No surgical resection	45	13.8 (9.8-16.7)	56%	17%	1	–	.182
Surgical resection	4	22.2 (13.6-infinity)	100%	38%	0.45	0.13-1.49	
No baseline PET avidity	12	18.8 (9.0-35.5)	75%	40%	1		.028
Baseline PET avidity	35	13.6 (9.8-14.8)	57%	11%	2.35	1.07-5.17	

Herman et al. Cancer 2015

Original Article

SE

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]

BACKGROUND: As systemic therapy has improved for locally advanced pancreatic cancer (LAPC), efforts to improve local control with optimal radiotherapy may be critical. Although conventionally fractionated radiation therapy (CFRT) has more recently shown a limited role in LAPC, stereotactic body radiation therapy (SBRT) is an emerging approach with promising results. With no studies to date comparing SBRT with CFRT for LAPC, this study used the National Cancer Data Base (NCDB) to evaluate these 2 modalities. **METHODS:** With the NCDB, patients with American Joint Committee on Cancer cT2-4/N0-1/M0 adenocarcinoma of the pancreas diagnosed from 2004 to 2013 were analyzed. Radiation therapy delivered at ≤2 Gy was deemed CFRT, and radiation therapy delivered at ≥4 Gy per fraction was considered SBRT. Kaplan-Meier analysis, log-rank testing, and multivariate Cox proportional hazards regression were performed with overall survival (OS) as the primary outcome. Propensity score matching was used. **RESULTS:** Among 8450 patients, 7819 (92.5%) were treated with CFRT, and 631 (7.5%) underwent SBRT. Receipt of SBRT was associated with superior OS in the multivariate analysis (hazard ratio, 0.84; 95% confidence interval, 0.75-0.93; $P<.001$). With propensity score matching, 988 patients in all were matched, with 494 patients in each cohort. Within the propensity-matched cohorts, the median OS (13.9 vs 11.6 months) and the 2-year OS rate (21.7% vs 16.5%) were significantly higher with SBRT versus CFRT ($P=.0014$). **CONCLUSIONS:** In this retrospective review using a large national database, SBRT was associated with superior OS in comparison with CFRT for LAPC, and these findings remained significant in a propensity-matched analysis. Further prospective studies investigating these hypothesis-generating results are warranted. ***Cancer* 2017;000:000–000.** © *2017 American Cancer Society.*

KEYWORDS: intensity modulated radiation therapy (IMRT), pancreatic cancer, radiation therapy (RT), stereotactic body radiation therapy (SBRT).

Zhong et al. Cancer 2017 (online)

SBRT vs. CFRT

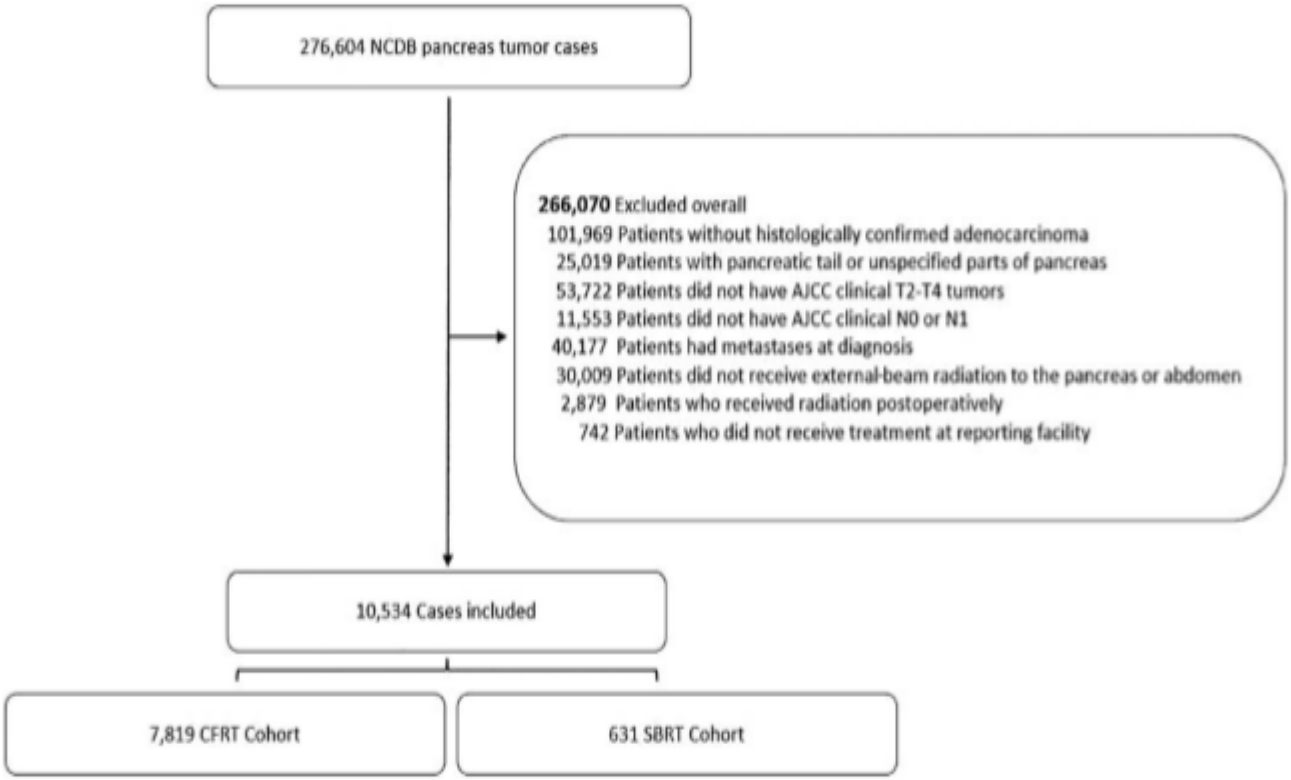


Figure 1. Patient Consolidated Standards of Reporting Trials diagram. AJCC indicates American Joint Committee on Cancer; CFRT, conventionally fractionated radiation therapy; NCDB, National Cancer Data Base; SBRT, stereotactic body radiation therapy.

Zhong et al. Cancer 2017 (online)

SBRT vs. CFRT

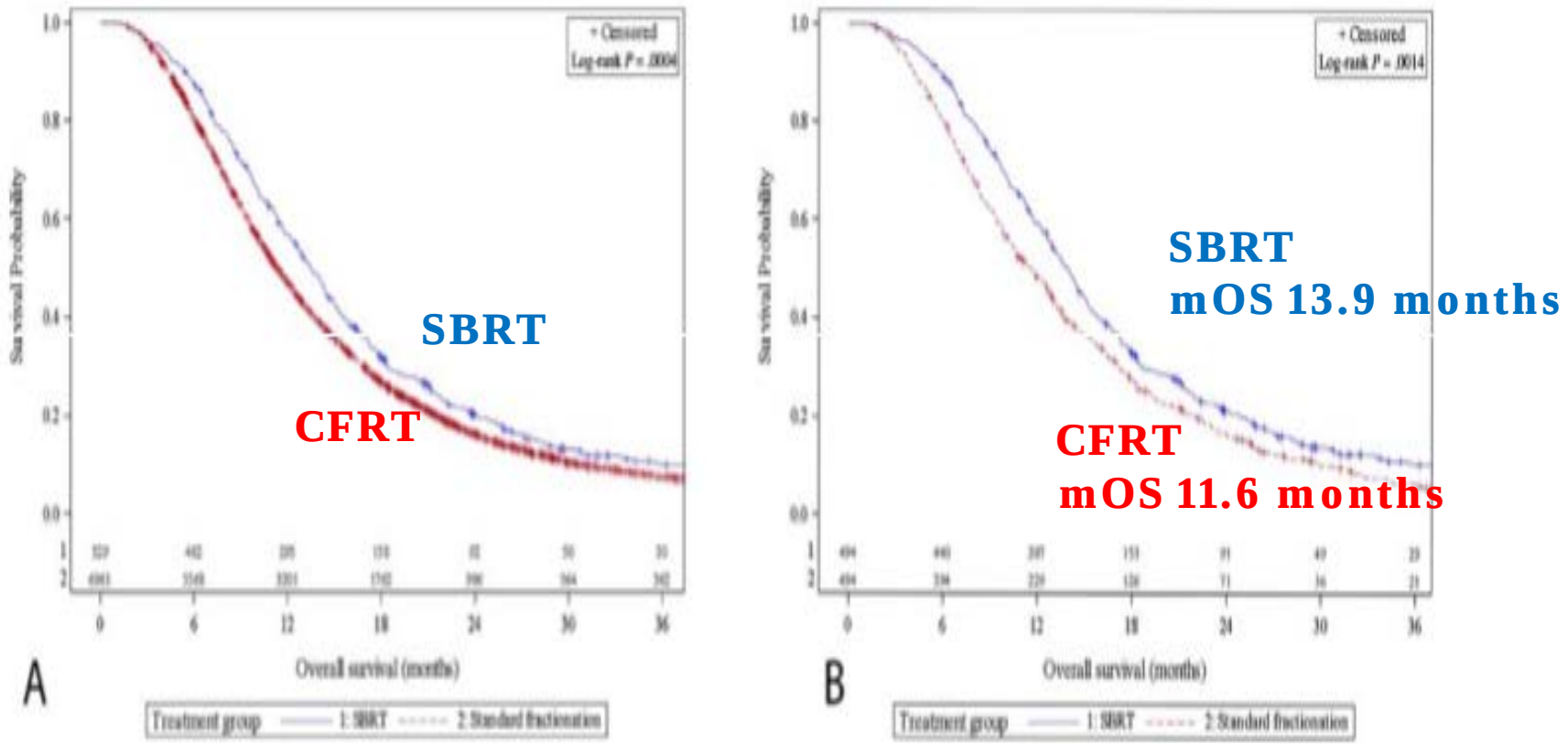
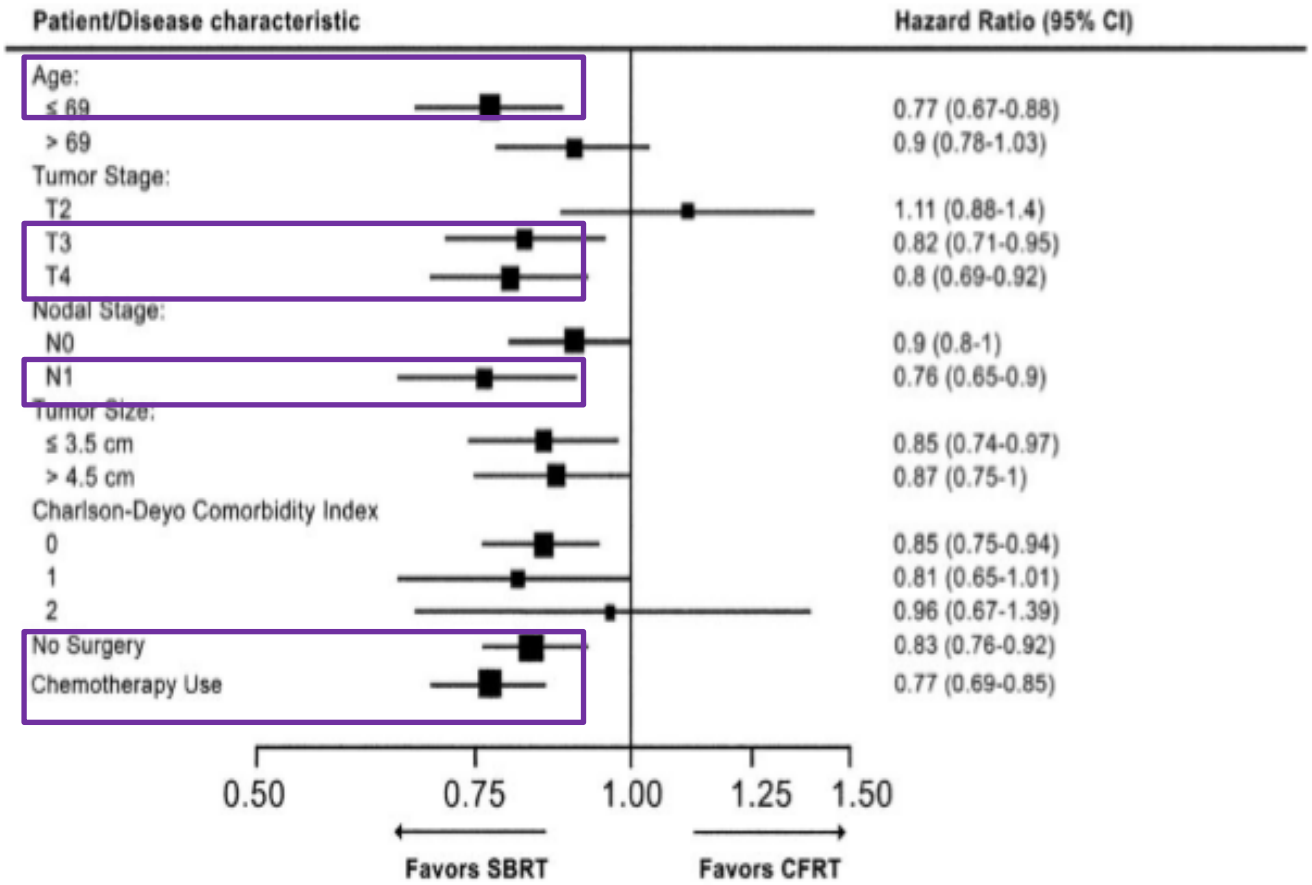


Figure 2. Kaplan-Meier curves demonstrating overall survival for (A) unmatched cohorts and (B) propensity-matched cohorts. SBRT indicates stereotactic body radiation therapy.

Zhong et al. Cancer 2017 (online)

SBRT vs. CFRT (subgroup analysis)



Zhong et al. Cancer 2017 (online)

Systematic review of SBRT for locally advanced CA pancreas

Critical Review

Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials

Fausto Petrelli, MD,* Tiziana Comito, MD,† Antonio Ghidini, MD,‡ Valter Torri, MD,§ Marta Scorsetti, MD,† and Sandro Barni, MD*

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Petrelli et al. IJROBP 2017

Table 2 Technical issues of radiation therapy in the included trials

Investigator	GTV delineation	PTV	4D-CT scan or motion tracking	Fiducial markers	Abdominal compression
Boone et al (14), 2013	Biphasic CT, PET	NR	NR	Yes	NR
Chuong et al (15), 2013	Biphasic CT	GTV + 3-5 mm	Yes	Yes	Yes
Didolkar et al (16), 2010	Biphasic CT, PET	GTV + 3 mm	Yes	Yes	No
Goyal et al (17), 2012	Biphasic CT, PET, MRI	NR	Yes	Yes	No
Gurka et al (18), 2014	Biphasic CT	GTV + adjacent vasculature without expansion	Yes	Yes	No
Herman et al (19), 2014	Biphasic CT, PET	GTV + 2-3 mm of margin	Yes	Yes	Yes
Hoyer et al (20), 2005	Biphasic CT	GTV + 5 mm in transverse and 10 mm in craniocaudal direction	Yes	No	Yes
Kim et al (21), 2013	Biphasic CT	GTV + 2 mm of margin	Yes	Yes	No
Lin et al (22), 2014	Biphasic CT	GTV + 5 mm of margin	Yes	Yes	Yes
Mahadevan et al (23), 2011	Biphasic CT	GTV + 5 mm of margin	Yes	Yes	No
Moningi, 2015	Biphasic CT, PET, MRI	GTV + 2-3 mm of margin	Yes	Yes	No
Polistina et al (25), 2010	Biphasic CT	GTV + 2 mm of margin	Yes	Yes	No
Pollom et al (26), 2014	Biphasic CT, PET	GTV (ITV) + 2-3 mm of margin	Yes	Yes	No
Rajagopalan et al (27), 2013	Biphasic CT	GTV + 2 mm of margin	Yes	Yes	No
Rwigema et al (28), 2011	Biphasic CT	GTV +2 mm of margin	Yes	Yes	No
Song et al (30), 2015	Biphasic CT	GTV+3 mm	Yes	Yes	No
Su et al (31), 2015	Biphasic CT scan	GTV +2 mm of margin	Yes	Yes	Yes
Tozzi et al (24), 2013	Biphasic CT, PET, MRI	GTV + 5 mm in transverse and 7 mm in craniocaudal direction	Yes	No	Yes
Mellon et al (24), 2015	Biphasic CT	GTV + 3-5 mm of margin	Yes	No	No

Abbreviations: 4D = 4-dimensional; CT = computed tomography; GTV = gross tumor volume; ITV = internal tumor volume; MRI = magnetic resonance imaging; NR = not reported; PET, positron emission tomography; PTV = planning target volume.

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Concurrent ChT (%)	FU (mo)	ORR (%)	LRC 1-2 y (%)	Median PFS (mo)	Median OS (mo) (OS 1-2 y)	G3-4 toxicity: acute, chronic (%)	Surgery (%)	Pre-, post-SBRT ChT, % (type)	BED10
No	<9	NR	NR	NR	NR	NR with SBRT	BRPC: 50 ChT + SBRT (R0) ULAPC: 0 ChT + SBRT (n=1 explored but not resected)	100 Pre- + 31 post-SBRT (FOLFIRINOX)	79.2
No	10.5	NR	81-NR	9.8 (LAPC) 9.7 (BRPC)	15 (LAPC) 16.4 (BRPC)† (72.2-68.1 BRPC and ULAPC 1 y)	0, 5.3 (bleeding, anorexia)	56.1 BRPC; 0 ULAPC (96.9% R0)	100 Pre- + 83.6 post-SBRT (GE-based 95%, FOLFIRINOX 5%)	59.5-100
No	NR	NR	50-NR	NR	13.4§ (n=35 no previous RT or surgery)	Duodenitis, gastritis, diarrhea (22.3), NR	0	56 Pre- + 100 post-SBRT (GE-based)	37.5-52.5
No	14.57	NR	65-NR	NR	14.37† (56%/1 y)	GI ulcers (16), GI ulcers (11)	0	68 Pre-SBRT (various regimens)	37.5-120
89	NR	NR	NR (~68, 1 y)	6.8	12.3†	abdominal pain (5)/GI hemorrhage (2.6)	0	11 Post-SBRT (GE- or 5-FU-based)	37.5-48
No	13.9	NR	78-NR	7.8	13.9† (59-18, 1-2 y)	GI ulcer (2); hematologic (12); other (4); fistula, ulcer (8); other (4)	8 (100% R0) 2% pCR	90 Pre-SBRT (GE alone)	53.7
No	NR	NR	57-NR	4.8	5.7† (5% at 1 y)	Ulceration (23), nausea (18), diarrhea (9), pain (36), NR	0	No	112.5
No	11.6	NR	41.2-NR	8.4 (FFMD)	7.6† (34.6% at 1 y)	0	0	15 Pre- + 23 post-SBRT (GE alone)	81.6-79.2
70	16	NR	70-50	NR	20† (80% at 1 y)	0	0	70 concurrent? (5-FU-based 85%)	59.5-85.5
No	21	NR	NR	15	20§	0, Bleeding, obstruction (7.6)	0	100 Pre- + 83 post-SBRT (GE alone)	43.2-79.2
No	13.1	NR	61-14	9.9	18.4§ (18.4 and 14.4 ULAPC and BRPC) 60 and 15 at 1-2 y	Ulcer, gastritis, other (4.5); ulcer, fistula bleeding (5.7)	21.5 (84% R0) 20% (ULAPC)	88 Pre- + 100 post-SBRT (GE-based 76%, FOLFIRINOX 24%)	37.5-53.6
No	9	69.6	NR	7.3 (TTP)	10.6 (39.1, 0 at 1-2 y)	0	8	100 Pre- + 100 post-SBRT (GE alone)	60
No	7.9	NR	89.3-NR	NR	13.6§ (33.1 at 1 y)	GI toxicity (12.3 at 12 mo)	NR	87.5 Pre- and/or post-SBRT (GE-based 95%, FOLFIRINOX 5%)	87.5
No	16.6	NR	NR	27.4	47.2§ (92, 64, 51 at 1, 2, and 3 y)	0	100 (92% R0) 25% pCR	91.7 Pre- + 75 post-SBRT (NS)	81.6 (60-79.2)
No	6	NR	38-NR*	NR	6.2* and 10.2† for whole cohort (32.6 at 1 y)	Nausea, abdominal pain, gastroparesis (4.2)‖, 0	NR	87 Pre- + 90 post-SBRT (GE-based 80%, 5-FU-based 20%)	50.4-81.6

Dose escalation of SBRT

Qing et al. Radiation Oncology (2017) 12:6
DOI 10.1186/s13014-016-0760-1

Radiation Oncology

STUDY PROTOCOL Open Access

Dose escalation of Stereotactic Body Radiotherapy (SBRT) for locally advanced unresectable pancreatic cancer patients with CyberKnife: protocol of a phase I study

Shui-Wang Qing, Xiao-Ping Ju, Yang-Sen Cao and Huo-Jun Zhang*

Qing et al. Radiat Oncol 2017

Dose escalation of SBRT

Abstract

Background: Dose escalation of SBRT for locally advanced pancreatic cancer patients had been reported in several studies in one or three fractions, and phase I protocol was developed to investigate the maximum tolerated dose with CyberKnife for locally advanced unresectable pancreatic cancer patients in five fractions.

Methods: The study is designed as a mono-center phase I study. The primary endpoint is to determine the maximum tolerated dose by frequency of III/IV GI (gastrointestinal) toxicity. Adverse events (AE) according to Common Toxicity Criteria (CTC) version 4. Doses of 7 Gy, 7.5 Gy, 8 Gy, 8.5 Gy, 9 Gy, 9.5Gy x 5 respectively would be delivered while meeting with normal tissue constraints. A minimum of three patients will be included for each dosage level. And an interval is 4 weeks from the first patient treatment to the next patient treatment at each dose level. The maximal tolerated dose will be defined as the dose for which at least two patients in three, or at least three patients in nine, will present with a limiting toxicity.

Discussion: Since the dose and fractions of SBRT treatment for locally advanced pancreatic cancer patients are still unknown, we propose to conduct a Phase I study determining the maximum tolerated dose of CyberKnife SBRT for the treatment of locally advanced pancreatic tumor based on a 5 fractions treatment regimen. This trial protocol has been approved by the Ethics committee of Changhai hospital. The ethics number is 2016-030-01.

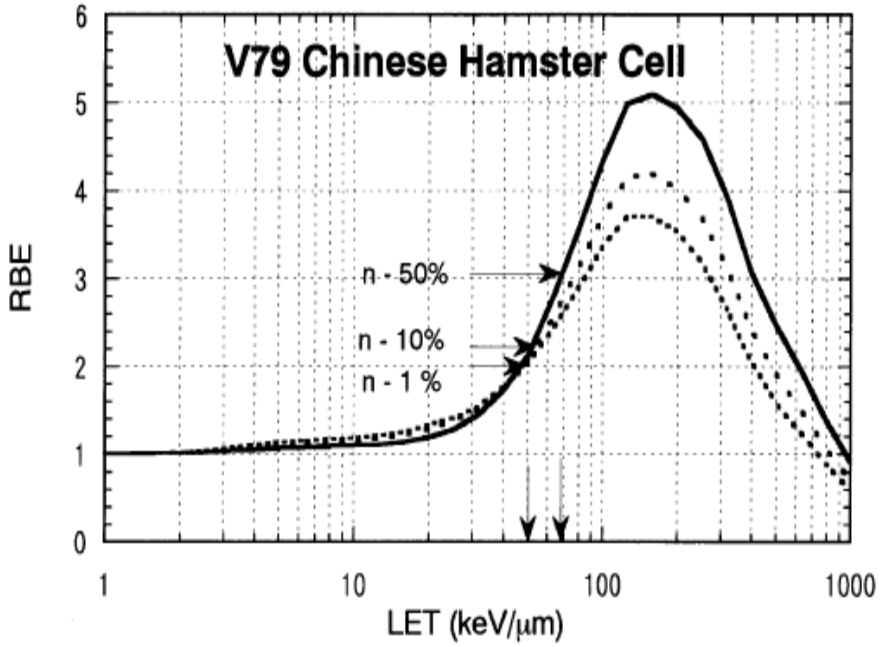
Trial registration: Clinical trials number: NCT02716207.
Date of registration: 20 March 2016.

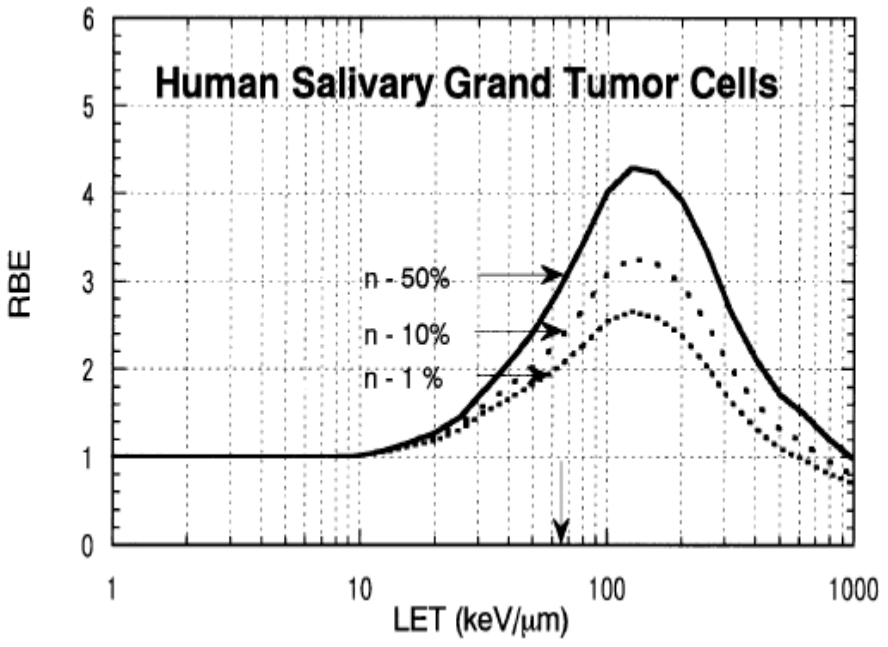
Keywords: Locally advanced pancreatic cancer, SBRT study protocol

Qing et al. Radiat Oncol 2017

Future directions (1)

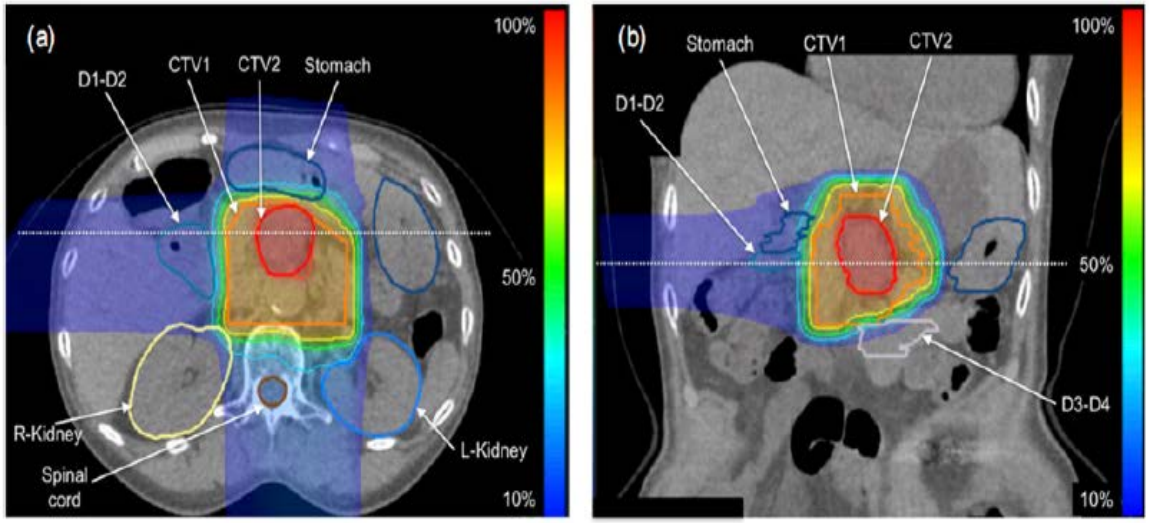
- Heavy ion therapy e.g. carbon ion with higher relative biological effectiveness (RBE) and linear energy transfer (LET) (3-4 times higher than x-rays, i.e. photon) leading to feasibility of further radiation dose escalation

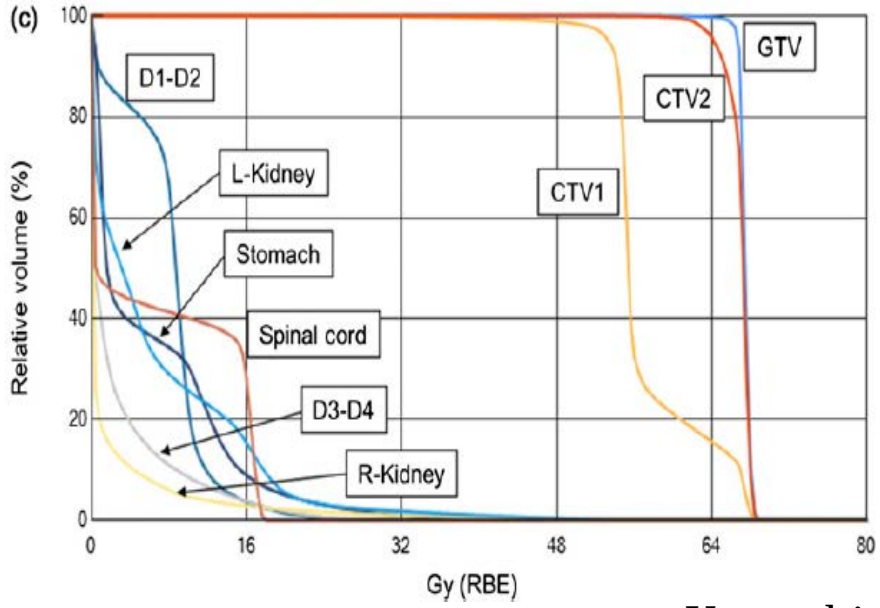




Kanai et al. IJROBP 1999

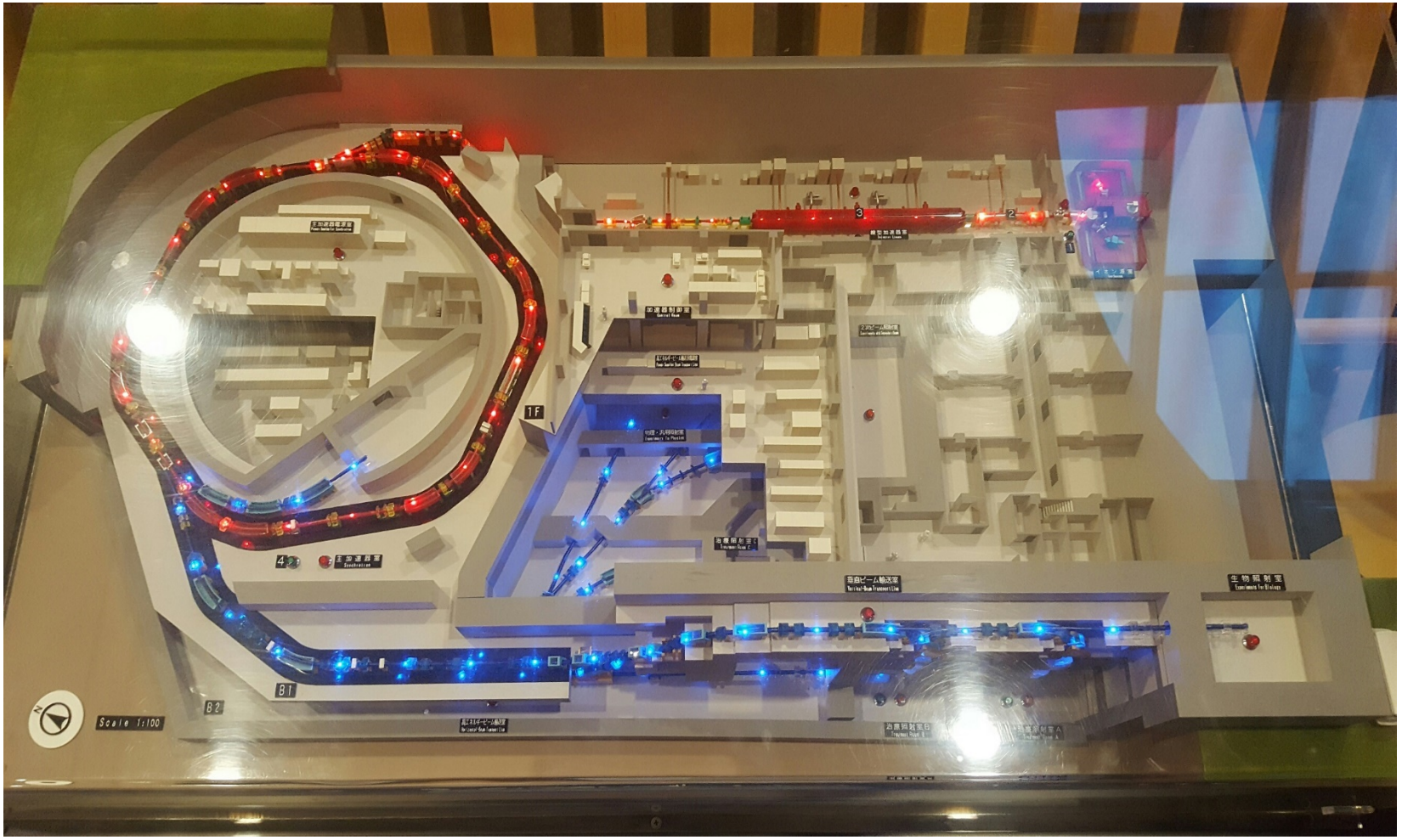
Carbon ion radiotherapy for LAPC





Kawashiro et al. BJR 2017 (online)

Carbon ion facilities at NIRS Japan



Carbon ion facilities at NIRS Chiba

Land in Hong Kong sold at 2.5b USD last week

美利道商業用地成新地王　恒地以232.8億元投得

2017-05-16 HKT 22:32

推介 0　分享工具

Future directions (2)

- SBRT combined with immune checkpoint inhibitors (against PD-1, PD-L1, CTLA-4 etc)

The NEW ENGLAND JOURNAL of MEDICINE

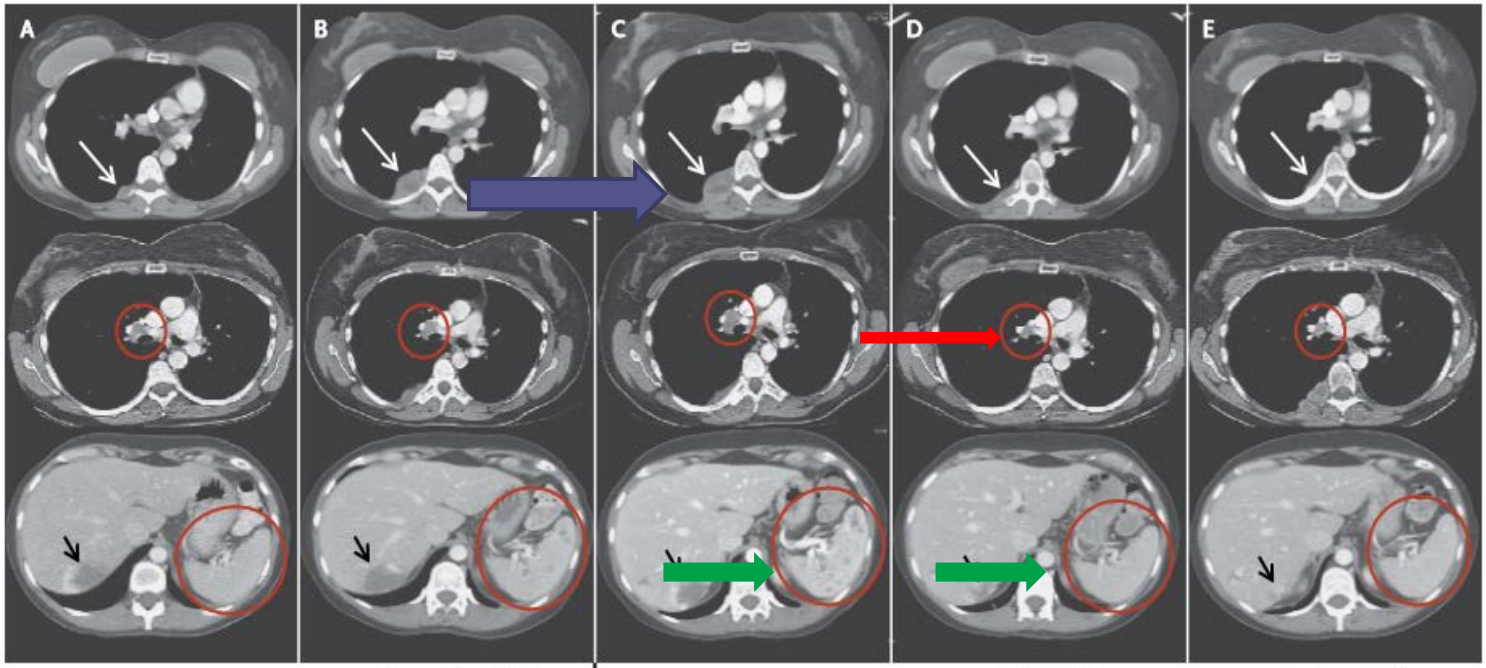
BRIEF REPORT

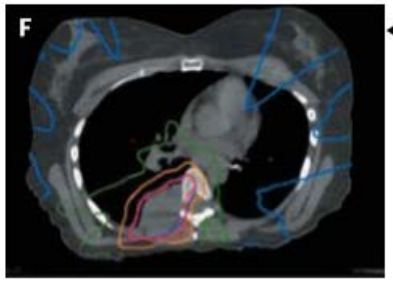
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

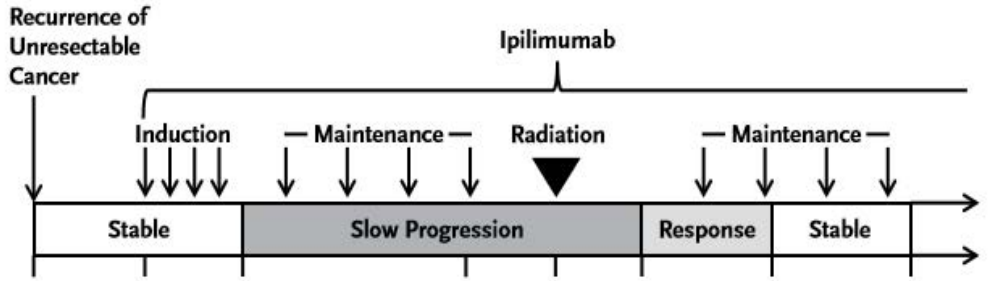
Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

Postow et al. NEJM 2012

Abscopal effect







Postow et al. NEJM 2012

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Trial record **1 of 1** for: pembrolizumab pancreas stereotactic

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Study With CY, Pembrolizumab, GVAX, and SBRT in Patients With Locally Advanced Pancreatic Cancer

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 by Sidney Kimmel Comprehensive Cancer Center

Sponsor:
Sidney Kimmel Comprehensive Cancer Center

Collaborator:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Sidney Kimmel Comprehensive Cancer Center

ClinicalTrials.gov Identifier:
NCT02648282

First received: January 5, 2016
Last updated: March 21, 2017
Last verified: March 2017
History of Changes

Study of Immune Checkpoint Inhibition With Radiation Therapy in Unresectable, Non-metastatic Pancreatic Cancer

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified February 2017 by New York University School of Medicine

Sponsor:
New York University School of Medicine

Collaborator:
AstraZeneca

Information provided by (Responsible Party):
New York University School of Medicine

ClinicalTrials.gov Identifier:
NCT02868632

First received: August 8, 2016
Last updated: February 27, 2017
Last verified: February 2017
History of Changes

Durvalumab (anti-PDL1) + tremelimumab (anti-CTLA4) + SBRT

Purpose

This is an open-label, three-cohort, phase Ib study to determine the safety, recommended phase 2 dose (RP2D), and efficacy of **Stereotactic Body Radiation** Therapy (SBRT) in combination with either (A) MEDI4736 alone, (B) tremelimumab alone, or (C) the combination of MEDI4736 and tremelimumab for patients with unresectable locally advanced adenocarcinoma of **pancreas**.

Condition	Intervention	Phase
Pancreatic Cancer	Drug: MEDI4736 Drug: Tremelimumab **Radiation**: **Stereotactic Body Radiation** Therapy (SBRT)	Phase 1

Study Type: Interventional

Study Design: Allocation: Non-Randomized
Intervention Model: Parallel Assignment
Masking: No masking
Primary Purpose: Treatment

Official Title: A Phase I Study of Immune Checkpoint Inhibition (Anti-CTLA4 and/or Anti-PD-L1) in Combination With **Radiation** Therapy in Patients With Unresectable and Non-metastatic **Pancreatic** Cancer

Available at ClinicalTrials.gov

Conclusion

- Chemoradiotherapy with standard fractionation is the standard treatment of locally advanced pancreatic cancer
- SBRT with or without concurrent chemotherapy may further escalate radiation dose to the tumours leading to better outcomes and more favourable toxicity profiles
- Accurate target delineation and tumour tracking is essential to the success of IGRT/SBRT
- Dose escalation by particle therapy and/or combination with immune checkpoint inhibitors may improve therapeutic ratio

Thank you


130
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