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Importance of daily adaption for the management of liver and pancreas patients receiving SBRT

AAPM 2021-SAM Session 7/25/2021

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Conflicts of Interest

- Nothing to disclose

Adaptive Radiation Therapy (ART)

- Many clinical scenarios we can adapt to
  - Anatomical adaptation
    - Intrafractional motion
    - Interfractional motion
    - Anatomical changes

"Radiotherapy where the delivered dose is monitored for clinical acceptability during the course of treatment and modified as needed with the goal of improving clinical outcomes."

Matuszak et al. 2019, Seminar Radiat Oncol

Adaptive Radiation Therapy (ART)

- Many clinical scenarios we can adapt to
  - Anatomical adaptation
    - Intrafractional motion
    - Interfractional motion
    - Anatomical changes
  - This presentation will focus on these characteristics

"Radiotherapy where the delivered dose is monitored for clinical acceptability during the course of treatment and modified as needed with the goal of improving clinical outcomes."

Matuszak et al. 2019, Seminar Radiat Oncol

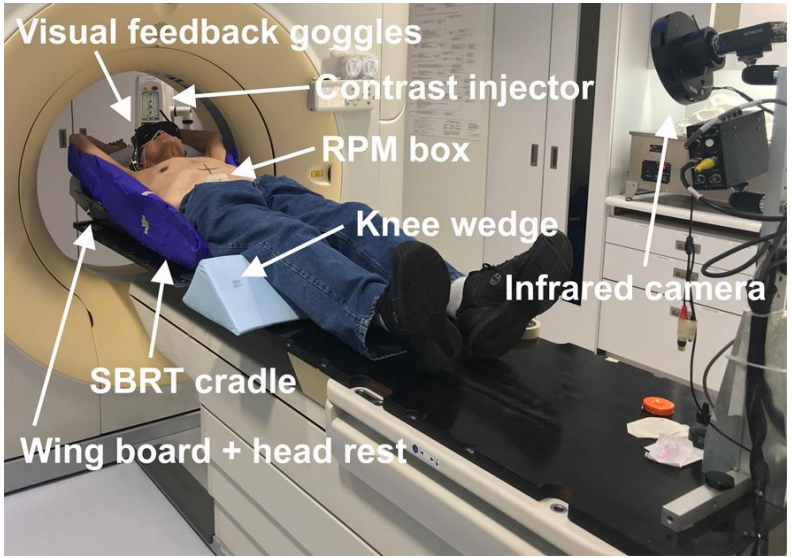
Outline

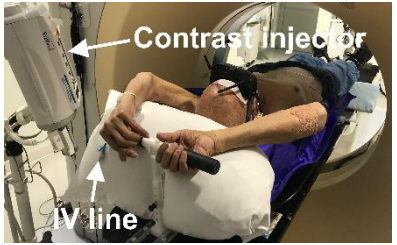
- CT-on-rails (CTOR) guided pancreas/liver SBRT at MDACC
- Dose-escalation & ART for liver/pancreatic cancer
  - Pancreas example
- Discussion

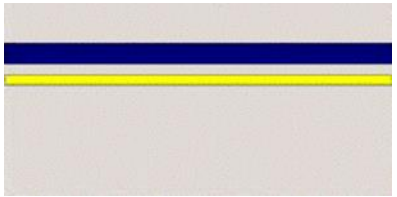
Pancreas/Liver Adaptive SBRT at MD Anderson

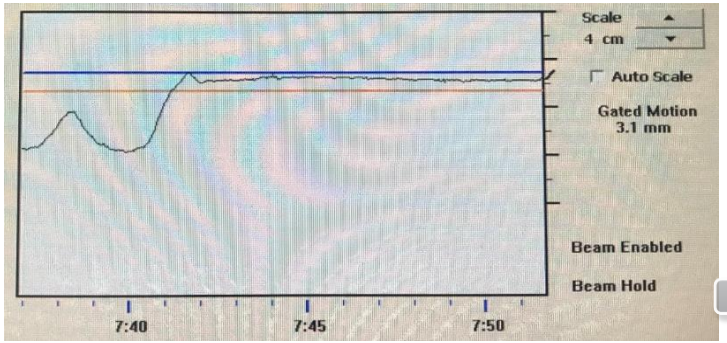
Pancreas/Liver SBRT at MD Anderson

Simulation









Pancreas/Liver SBRT at MD Anderson

Contrast-enhanced BHCTs

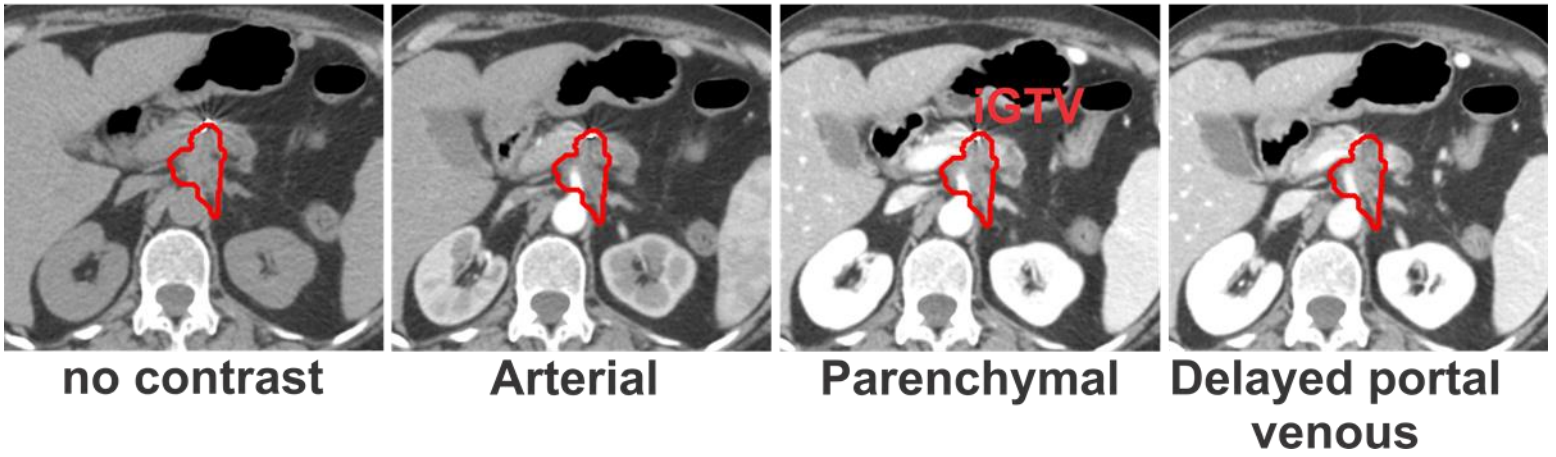


Figure courtesy of Peter Park, PhD

Pancreas/Liver SBRT at MD Anderson

Treatment Planning

- **Liver**
  - Rx = 50 Gy in 4 Fxs
- **Pancreas**
  - Rx for up to 3 PTVs
  - Rx 33-40Gy (high dose PTV)
  - Fiducial markers not typical

Normal Tissue Constraints

	Conv. RT	SBRT
Duodenum	D_{max} < 60 Gy	D_{max} < 40 Gy
	V54Gy < 1 cc	V35Gy < 1 cc
Small Bowel	D_{max} < 54 Gy	D_{max} < 40 Gy
	V45Gy < 1 cc	V35Gy < 1 cc
Large Bowel	D_{max} < 60 Gy	D_{max} < 40 Gy
	V54Gy < 1 cc	V35Gy < 1 cc
Stomach	D_{max} < 60 Gy	D_{max} < 40 Gy
	V54Gy < 1 cc	V35Gy < 1 cc
Liver	D_{mean} < 28 Gy	D_{mean} < 16 Gy
		aV15 < 700cc

Pancreas SBRT at MD Anderson

Treatment Planning

- Special ROIs: TVI, GI-PRV
- Rxs
  - 33, 36, 40 Gy common
- Variable PTV strategies
  - PTV 25: 25 Gy to GTV+3mm
  - PTV 33: 33Gy to GTV+3mm – GI-PRV
  - PTV 36: 36 Gy to TVI+3mm – GI-PRV

TVI: tumor vessel interface
GI-PRV: gastrointestinal planning organ at risk volume

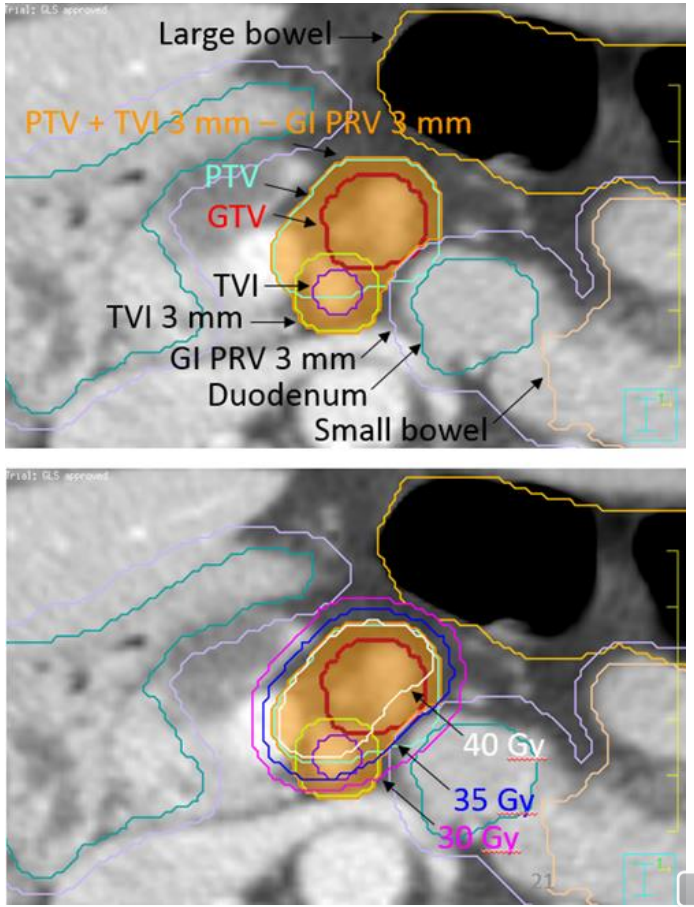
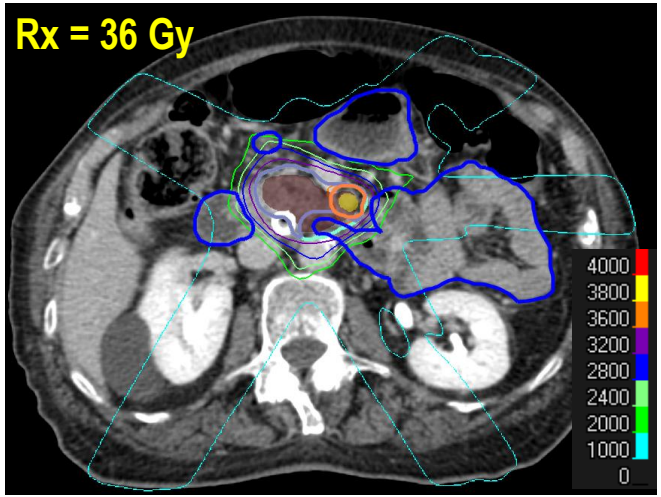
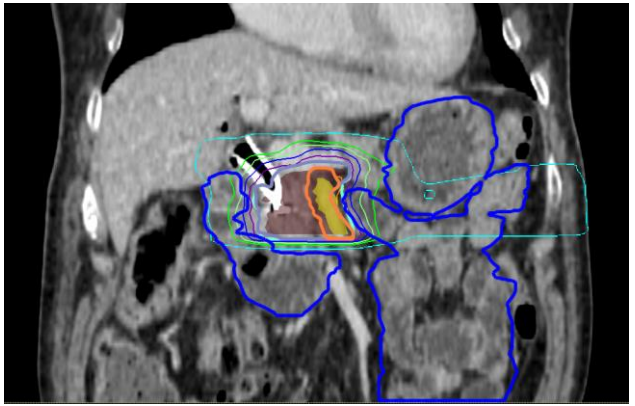
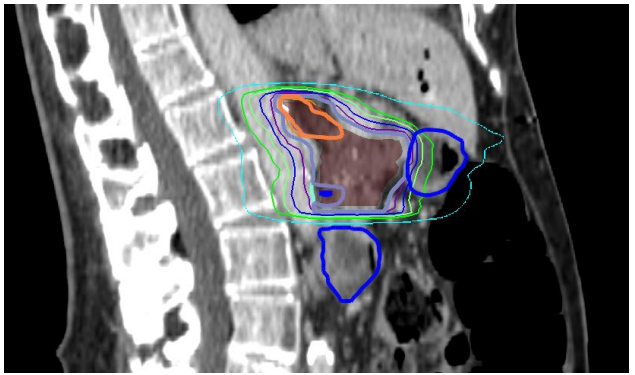


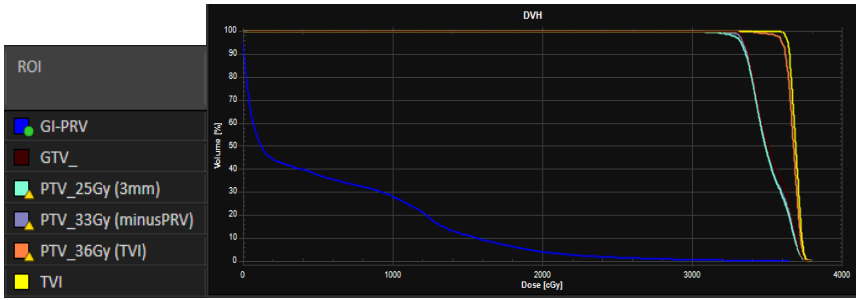
Image courtesy of Gabriel Sawakuchi, PhD

Pancreas/Liver SBRT at MD Anderson









Pancreas/Liver SBRT at MD Anderson

Treatment delivery

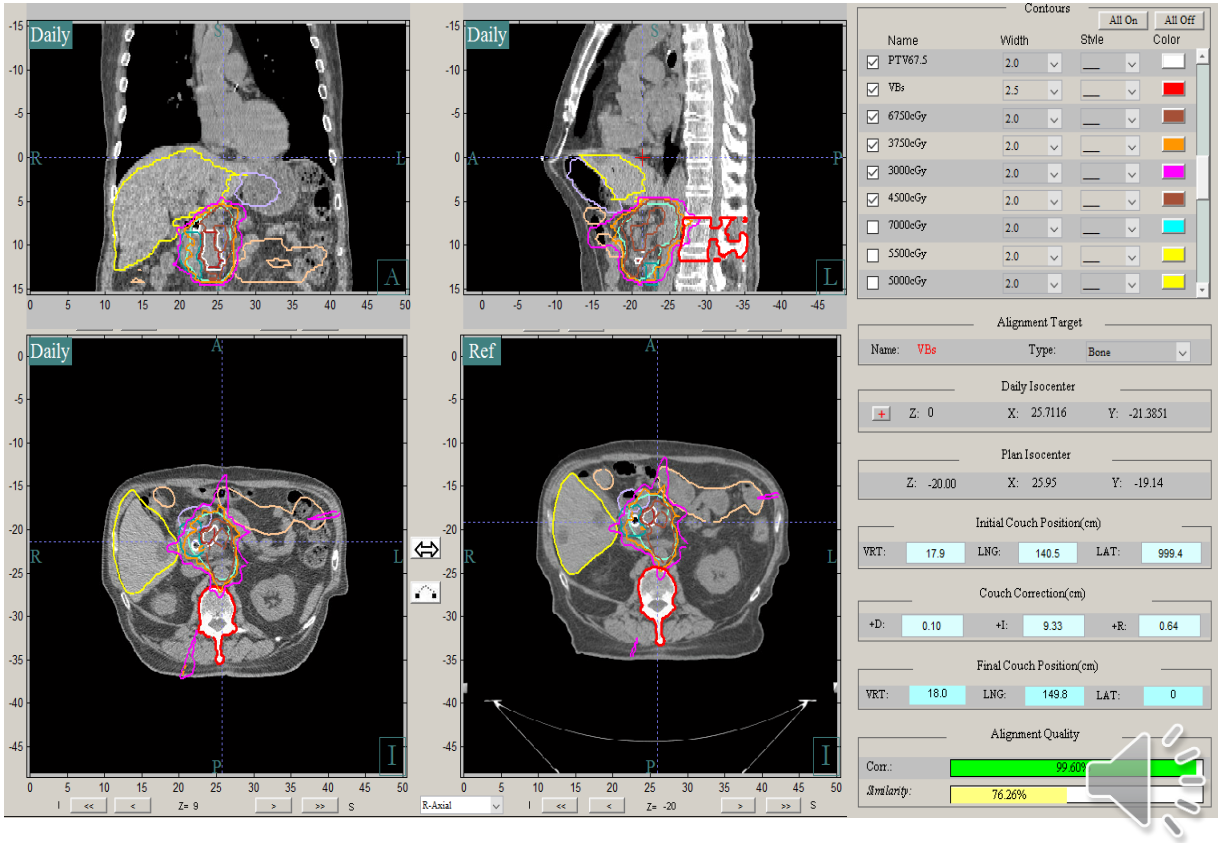
- NPO 3 hrs
- IMRT, varian 2100 series
- RPM respiratory breath-hold gating
- CT-on-rails, in-room CT for image guidance

Image courtesy of Gabriel Sawakuchi, PhD

Pancreas/Liver SBRT at MD Anderson

Image Guidance

- Load CTOR image
- Apply rigid alignment to VB
- Physician will align to target
- Planning isodose lines saved as ROIs for reference
- Allows avoidance of OARs & coverage of target



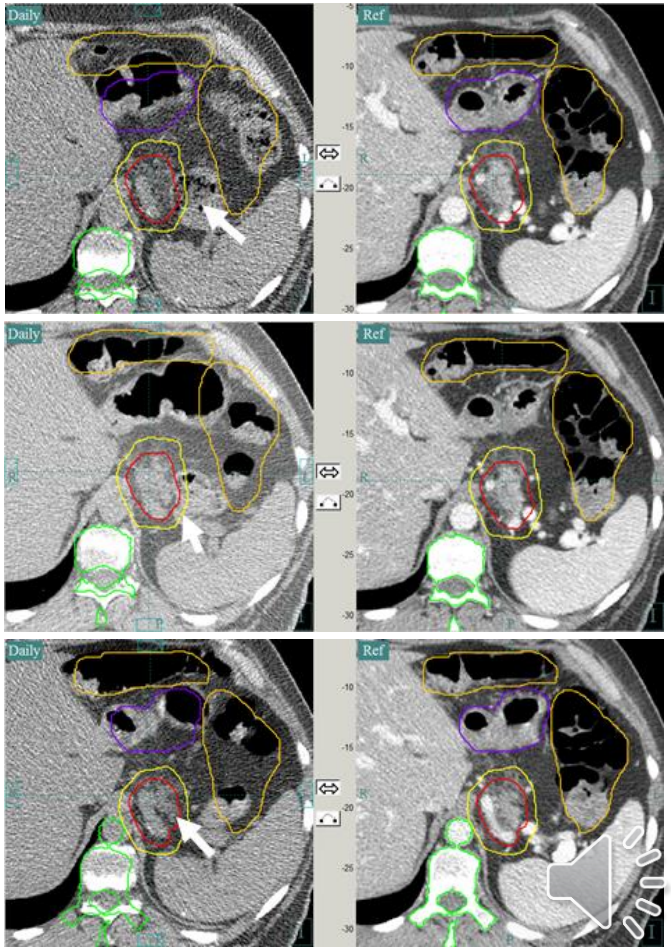
Pancreas/Liver SBRT at MD Anderson

Example of Image Guidance

Day 1: Bowel invading into high dose gradient (red & yellow isodose lines)

5 hours later: no improvement

Day 2: Bowel out of high dose gradient



Slide courtesy of Albert Koong, MD, PhD

Pancreas/Liver SBRT at MD Anderson

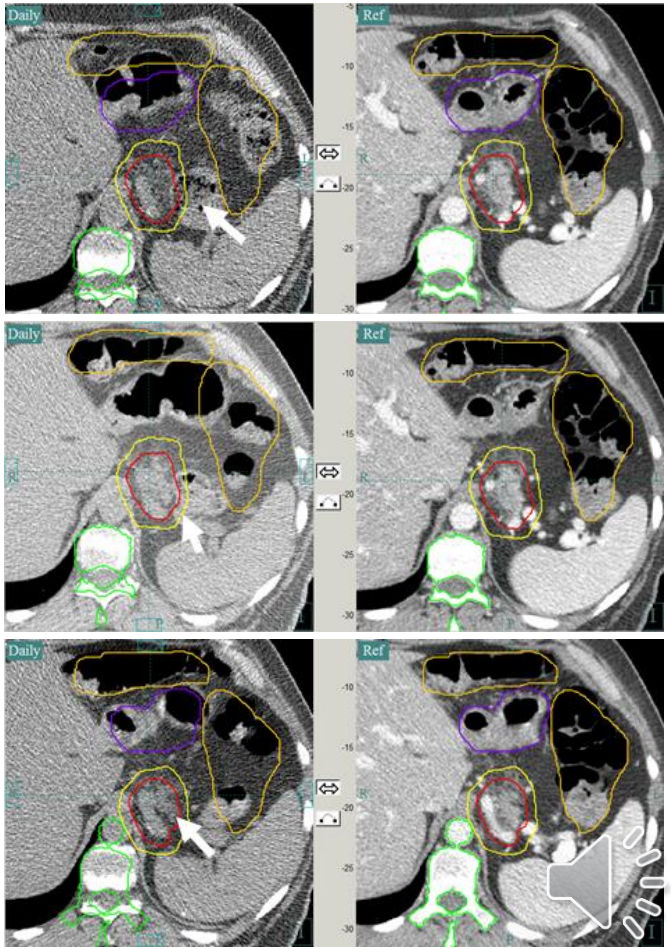
Example of Image Guidance

- Simple form of adaptation
- Only move couch (aka Tx Iso)
- No plan re-optimization

Day 1: Bowel invading into high dose gradient (red & yellow isodose lines)

5 hours later: no improvement

Day 2: Bowel out of high dose gradient

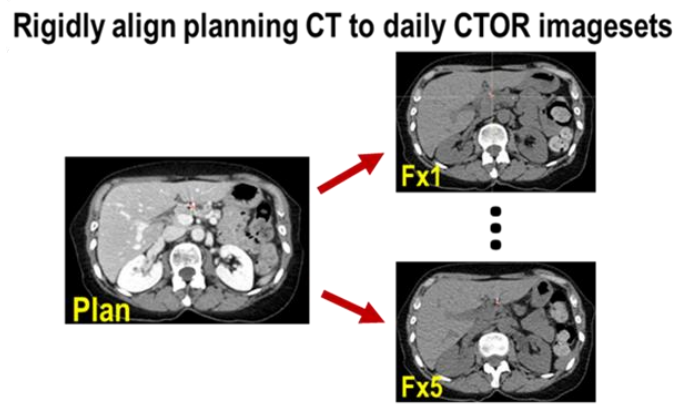


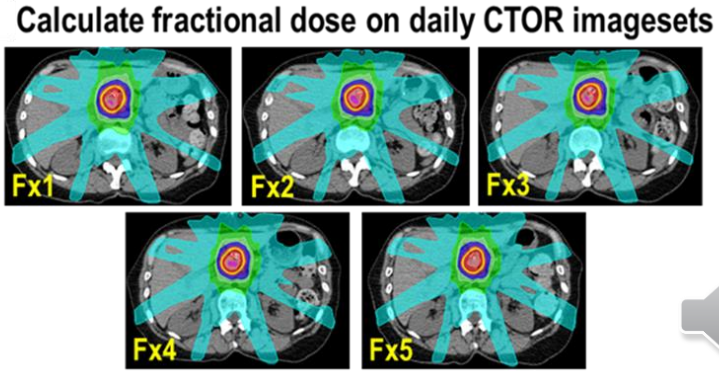
Slide courtesy of Albert Koong, MD, PhD

Simulated Daily ART Strategy (Pancreas)

Daily ART w/plan re-optimization

- Compare clinically planned SBRT dose to:
  1. Clinical delivered dose
  2. Daily re-optimized delivered dose
- Re-optimization strategy:
  - Maintain beam arrangement
  - Attempt to regain clinical plan target coverage
  - Maintain OAR constraints
  - Accumulate dose and compare
- 8 LAPC pts, 5-Fx SBRT Tx (Rx=33/36Gy)



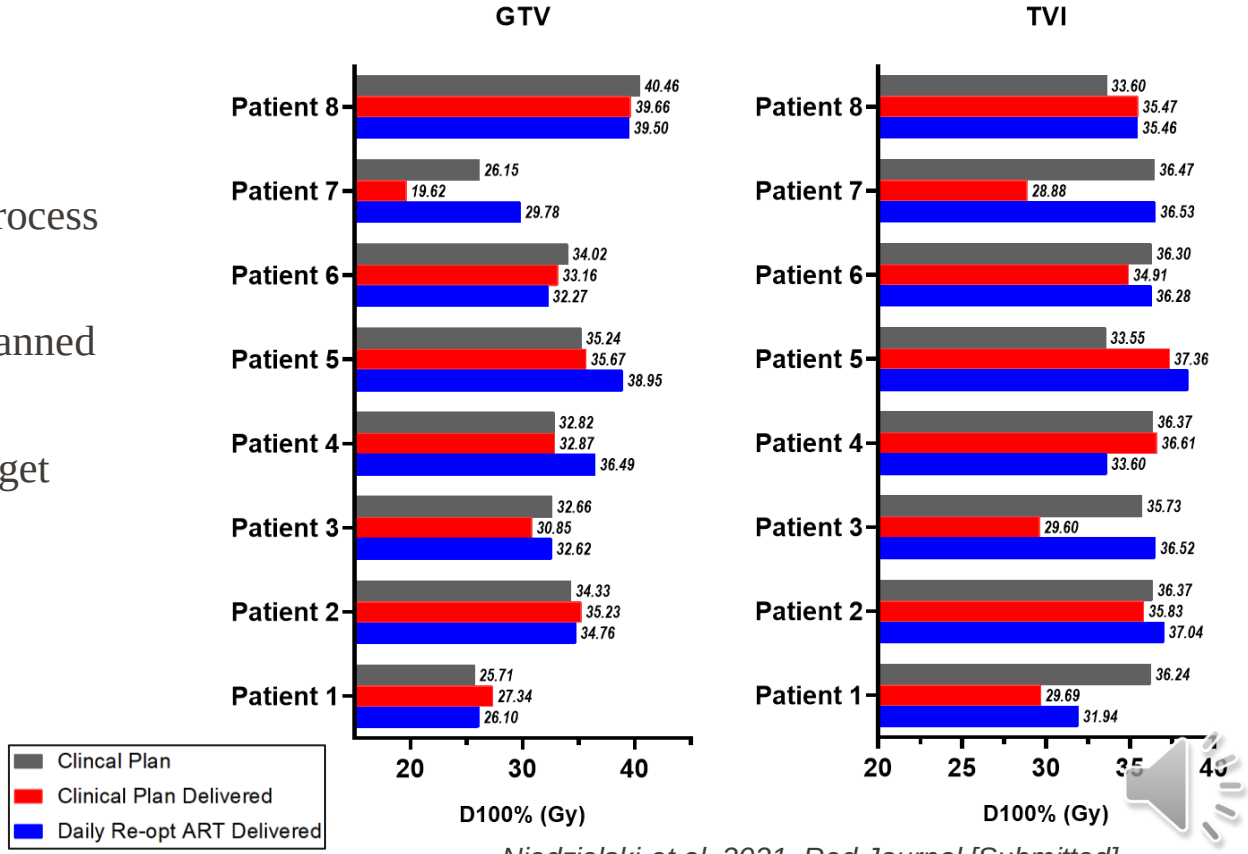


Niedzielski et al. 2021, Red Journal [Submitted]

Simulated Daily ART Strategy (Pancreas)

Results

- Re-optimization was a rapid process (~10 mins)
- Can be large difference b/w planned & delivered dose
- Re-optimization can regain target coverage for many patients



Niedzielski et al. 2021, Red Journal [Submitted]

Dose-Escalated SBRT for Liver and Pancreas Cancer

BED Comparisons

Tumor (α/β=10)		Number of Fractions					
		25	15	10	5	3	1
Rx Dose (Gy)	30.0	33.6	36.0	39.0	48.0	60.0	120.0
	33.0	37.4	40.3	43.9	54.8	69.3	141.9
	36.0	41.2	44.6	49.0	61.9	79.2	165.6
	40.0	46.4	50.7	56.0	72.0	93.3	200.0
	50.0	60.0	66.7	75.0	100.0	133.3	300.0
	60.0	74.4	84.0	96.0	132.0	155.8	357.5

BED Comparisons

STD RT

HYPO RT

SBRT

Tumor (α/β=10)		Number of Fractions					
		25	15	10	5	3	1
Rx Dose (Gy)	30.0	33.6	36.0	39.0	48.0	60.0	120.0
	33.0	37.4	40.3	43.9	54.8	69.3	141.9
	36.0	41.2	44.6	49.0	61.9	79.2	165.6
	40.0	46.4	50.7	56.0	72.0	93.3	200.0
	50.0	60.0	66.7	75.0	100.0	133.3	300.0
	60.0	74.4	84.0	96.0	132.0	155.8	357.5

RT Dose-escalation for Pancreatic Cancer

- *Krishnan et al. 2016 (Red Journal)*
  - LAPC (n=200), Induction Chemo + CRT
  - 47 received SIB to >70 Gy BED
  - DE arm had superior OS
    - 3-yr: 31% vs. 9%
- *Arcelli et al. 2020 (Anticancer Res)*
  - LAPC with SBRT (BED = 28-78 Gy)
  - BED > 48 Gy improved OS, LC
- *Reyngold et al. 2021 (JAMA Oncol)*
  - LAPC (n=119)
  - Ablative DE RT
  - BED = 98Gy
  - 1-yr FFLP = 82.4%
  - 1-yr OS = 74%

CRT: chemoradiation therapy
SBRT: stereotactic body radiation therapy
BED: Biological effective dose
LAPC: Locally advanced pancreas cancer

RT Dose-escalation for Liver Cancer

Table 2. Summary of HCC Radiotherapy Studies in Order of Local Control at 2 Years.[a]

Study, Year	n	CP-B %	Median Tumor Diameter, cm	Dose (Range) /fx	BED Gy_{10}	EQD2	Dose-Prescription Point	1-Year OS	2-Year LC
Yamashita, 2015[24]	79	11%	2.7	48 Gy/4-10	71-106	59-88	D95% PTV	78%	64%
Bujold, 2013[7]	102	0%	9.9	24-54 Gy/6	34-103	28-86	D95% PTV modified based on effective liver volume irradiated	75%	74%
Bibault, 2013[25]	75	11%	3.7	40-45 Gy/3	72-85	60-71	80% IDL D95% PTV	79%	90%
Andolino, 2011[26]	60	40%	3.1	30-48 Gy/3	60-125	50-104	80% IDL	82%[b]	90%
Jung, 2013[27]	92	26%	2.5	45 Gy/3-4	96-113	80-94	85-90% IDL	87%	92% (3 years)
Sanuki, 2013[28]	185	15%	2.7	40 Gy/5	72	60	70-80% IDL	95%	93%
Yoon, 2013[29]	93	26%	2.0	45 Gy/3-4	96-113	80-94	D100% PTV	86%	95%[b]
Takeda, 2014[30]	63	16%	2.6	35-40 Gy/5	60-72	50-60	70-80% IDL	100%	95%
Huertas, 2015[31]	77	14%	2.4	45 Gy/3	113	94	80% IDL	82%	99%
Kimura, 2015[32]	65	14%	1.6	48 Gy/4	106	88	Isocenter	NR	100%
Jang, 2013[22]	108	10%	3.0	51 Gy/3	138	115	70-80% IDL D97% PTV	83%[b]	100%

Abbreviations: BED, biologically equivalent dose; CP, Child-Pugh; EQD2, equivalent dose is 2 Gy fractions; fx, fractions; HCC, hepatocellular carcinoma; IDL, isodose line; LC, local control; n, patient number; NR, not reported; OS, overall survival; PTV, planning target volume.

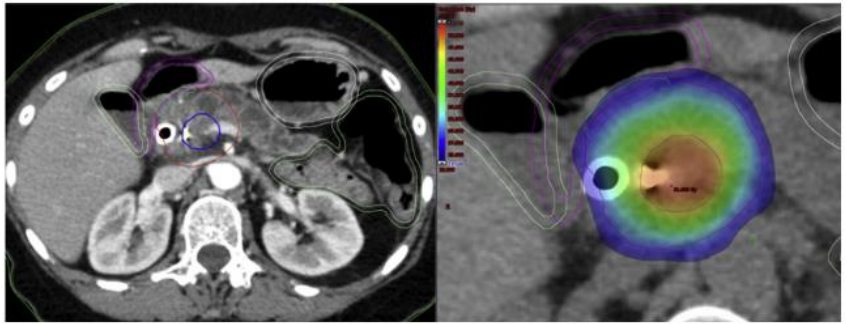
[a]Studies included were published between 2002 and 2017 with more than 50 patients with HCC and reporting 2-year local control.

[b]Estimated from survival curve.

Schaub et al. 2018, Technol Cancer Res Treat

Dose-escalation techniques

- Historically, modify the RT plan
  - Clinical data
  - Imaging data (tumor extent, motion, etc.)
  - Incorporating mulitple PTVs/CTVs & SIBs
  - Generally not an adaptive approach



Simoni et al. 2021, Clin Oncol

TABLE 5 | Studies using SBRT with Simultaneous Integrated Boost (SIB) for pancreatic cancer.

Reference	Fractions (n)	PTV definition	PTV dose	SIB target	SIB dose
Chuong et al. (26)	5	PTV = entire tumor + 3–5 mm	25 Gy	TVI (region of vessel abutment/encasement)	35 Gy
Mellon et al. (27)	5	PTV = GTV (plus motion) + 3–5 mm	30 Gy	TVI (areas of vessel involvement by tumor)	40 Gy
Shaib et al. (28)	3	PTV = GTV with at-risk area of microscopic spread + 5 mm	36 Gy	PM = volume between the posterior 1 cm of GTV and mesenteric vessel/retroperitoneal soft tissue	45 Gy
Holyoake et al. (29)	5	PTV = entire tumor + 5 mm	35 Gy	TVI (margin-directed boost)	50 Gy
Kharofa et al. (30)	5	PTV elective = PTV + customized nodal space and mesenteric vessels	25 Gy	PTV = GTV + TVI	33 Gy
Koay EJ et al. (31)	5	PTV = (GTV + TVI) + 3 mm	33 Gy	PTV_{high} = PTV with PRV OARs subtracted	50 Gy
Simoni et al. (12)	5	PTV = entire tumor + 5 mm	30 Gy	TVI (region of vessel abutment/encasement)	50 Gy

n, number; PTV, planning target volume; SIB, simultaneous integrated boost; Gy, gray; TVI, tumor-vessel interface; GTV, gross tumor volume; PM, posterior margin; PRV OARs, planning organs at risk volume.

Mazzarotto et al. 2020, Front Oncol

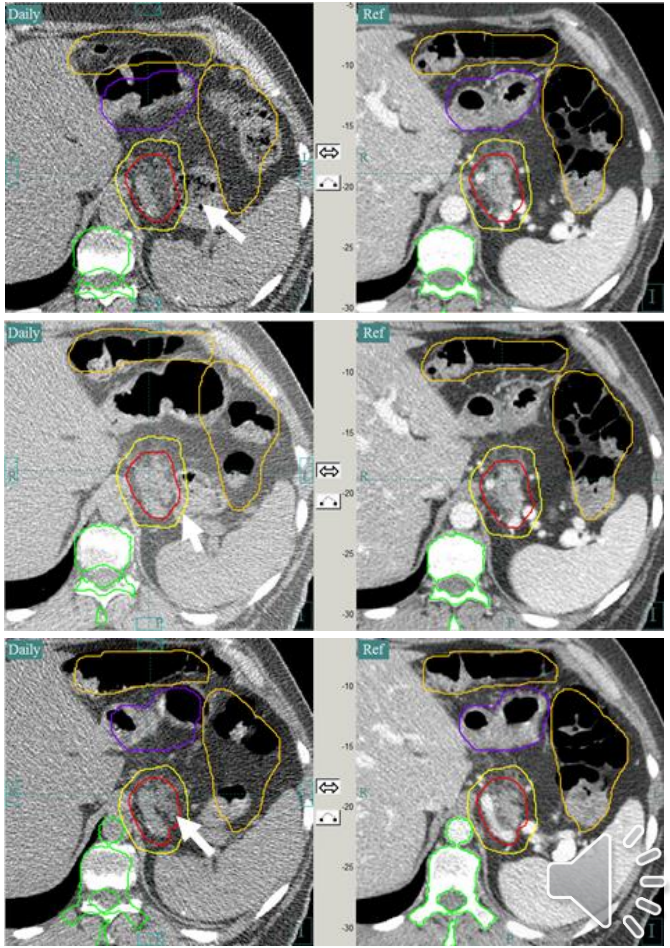
Dose-Escalation & Daily ART

- Daily adaptation and dose-escalation are synergistic
- Avoid target miss while preserving OAR constraints
- Ongoing studies, mainly for MR-linac (stay tuned, next talk!)

Day 1: Bowel invading into high dose gradient (red & yellow isodose lines)

5 hours later: no improvement

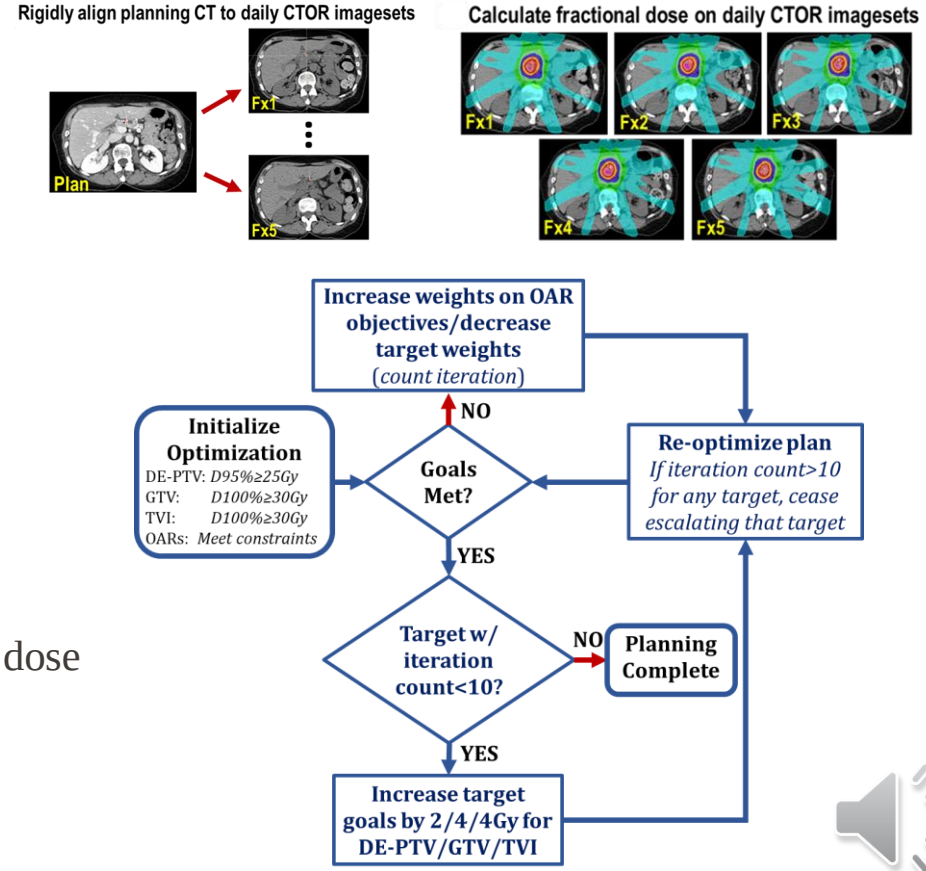
Day 2: Bowel out of high dose gradient



Dose-Escalation & Daily ART

Adaptive DE SBRT w/CTOR

- 8 LAPC pts, 5-Fx SBRT (Rx=33/36Gy)
- Iterative DE planning on each Fx
  - Re-plan on each Fx CTOR imageset
  - DE-PTV and SIBs to GTV &TVI
  - OAR constraints limit Rx
- Accumulate dose
- Compare to clinical plan & clinically delivered dose

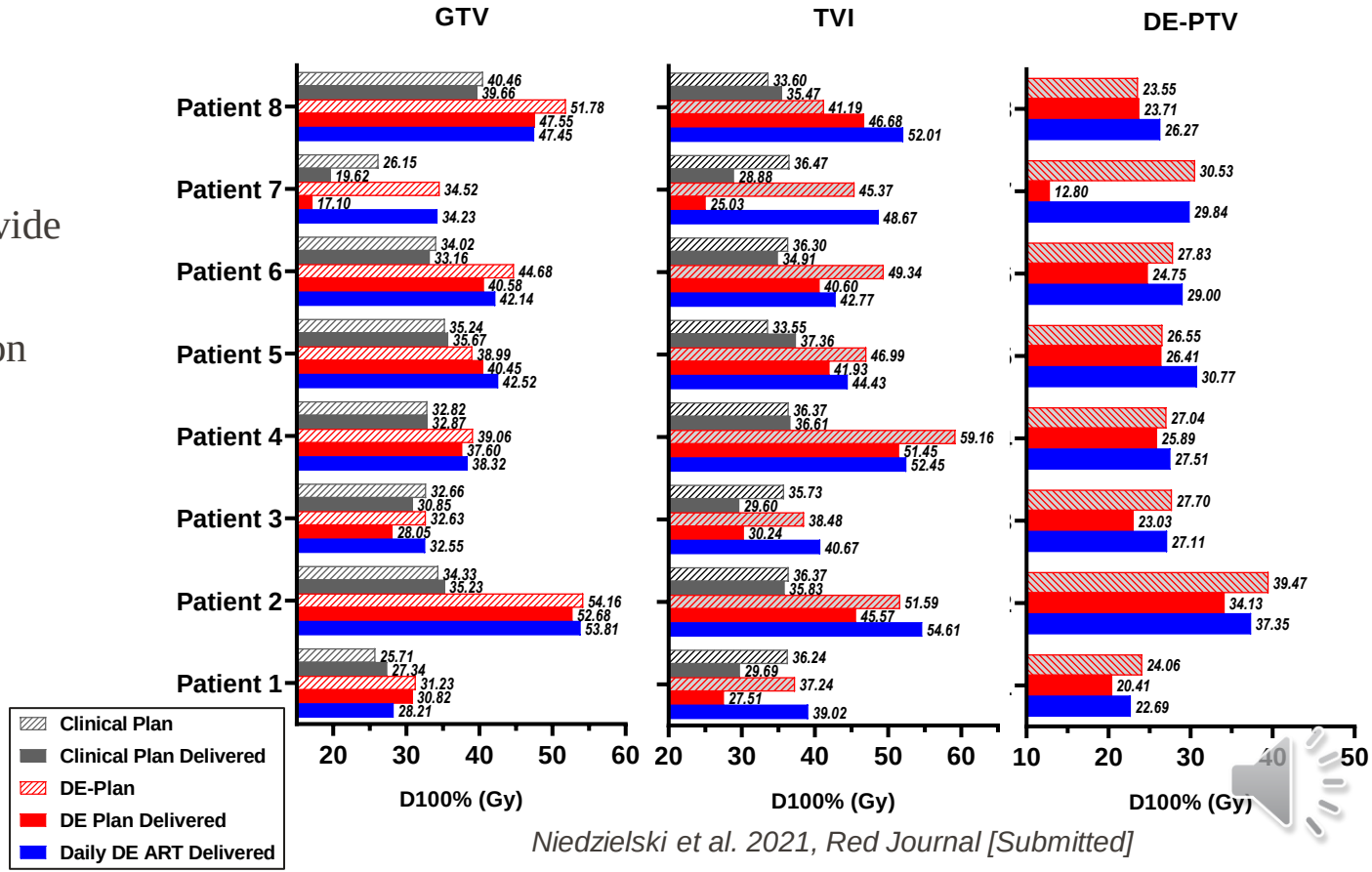


Niedzielski et al. 2021, Red Journal [Submitted]

Dose-Escalation & Daily ART

Results

- Iterative DE plans provide much higher coverage
- DE w/o daily adaptation can lose coverage
- Daily DE ART very similar to planned DE doses



Niedzielski et al. 2021, Red Journal [Submitted]

Final Thoughts

Discussion

- Adaptive SBRT has great potential for treating both liver & pancreatic cancer
- Interfractional motion is large hurdle for optimal treatments
  - Image guidance is critical
- Adaptive approaches show promise in remedying interfractional motion effects
- Combined dose-escalation and adaptive strategies show great promise
  - High quality imaging is pivotal component → MR-linac…
  - Intrafractional motion must also be considered → MR-linac…

References

- Matuszak MM, et al. Functional Adaptation in Radiation Therapy. Semin Radiat Oncol. 2019;29.
- Krishnan S, et al. Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation. Int J Radiat Oncol Biol Phys. 2016;94(4):755–765.
- Arcelli A, et al. Stereotactic body radiotherapy vs conventionally fractionated chemoradiation in locally advanced pancreatic cancer: A multicenter case-control study (PAULA-1). Cancer Med. 2020;9(21):7879–7887.
- Reyngold M, et al. Association of Ablative Radiation Therapy With Survival Among Patients With Inoperable Pancreatic Cancer. JAMA Oncol. 2021.
- Schaub SK, et al. Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Current Trends and Controversies. Technol Cancer Res Treat. 2018 Jan 1;17:1533033818790217. Siegel RL, et al. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7-33.
- Simoni N, et al. Hypofractionated Stereotactic Body Radiation Therapy With Simultaneous Integrated Boost and Simultaneous Integrated Protection in Pancreatic Ductal Adenocarcinoma. Clin Oncol. 2021;33(1):e31-e38.
- Mazzarotto R, et al. Dosimetric Feasibility Study of Dose Escalated Stereotactic Body Radiation Therapy (SBRT) in Locally Advanced Pancreatic Cancer (LAPC) Patients: It Is Time to Raise the Bar. Front Oncol. 2020;10(December):1-9.

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