What We Know and Don't Know About Re-Irradiation: Review of the Literature

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Outline

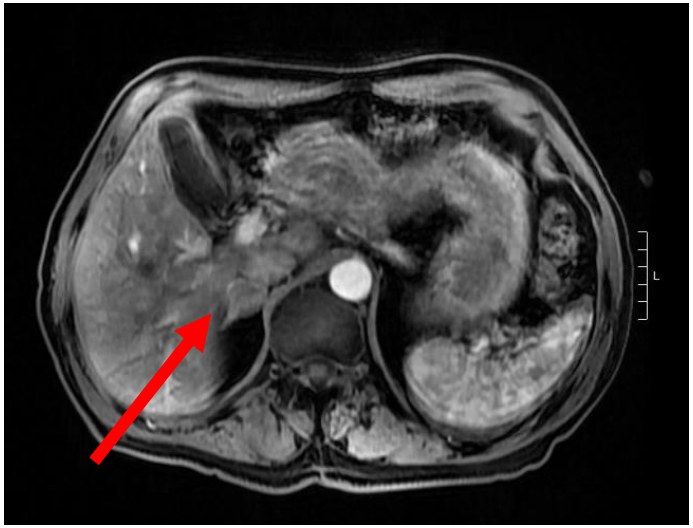
- Scope of the re-irradiation challenge
- How do we determine whether re-irradiation would be safe?
  - Real-world example
  - Data
    - Data on safe and unsafe re-irradiation
    - Understanding error bars

Scope of the re-RT challenge

- Re-irradiation used to be uncommon
- As systemic therapy improves, patients are living longer
- Challenges:
  - For our field: Determining (relatively) safe limits for re-treatment
  - For individuals: Applying these limits to clinical practice

Case

- 73 year old patient with uveal melanoma s/p plaque in 2000
- 12/2017 treated with 3600 cGy in 12 fractions to peripancreatic nodes and left adrenal metastasis.
- He comes for a consult, bringing a new scan showing a new right adrenal metastasis.

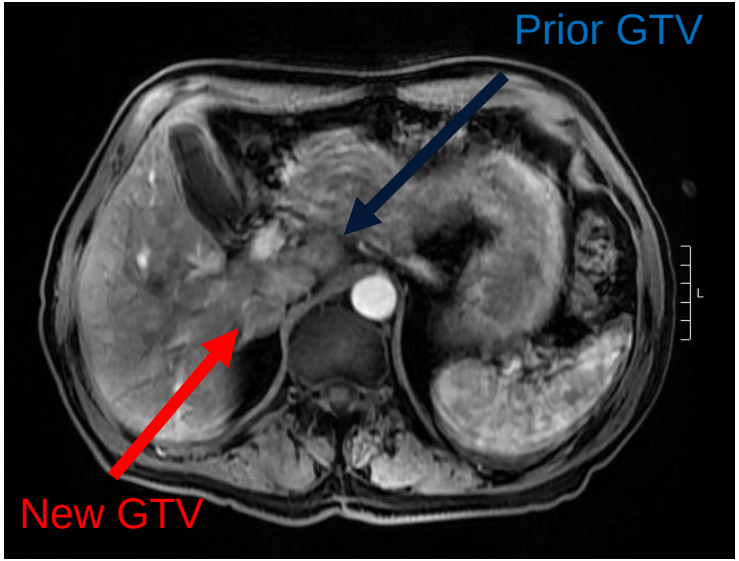


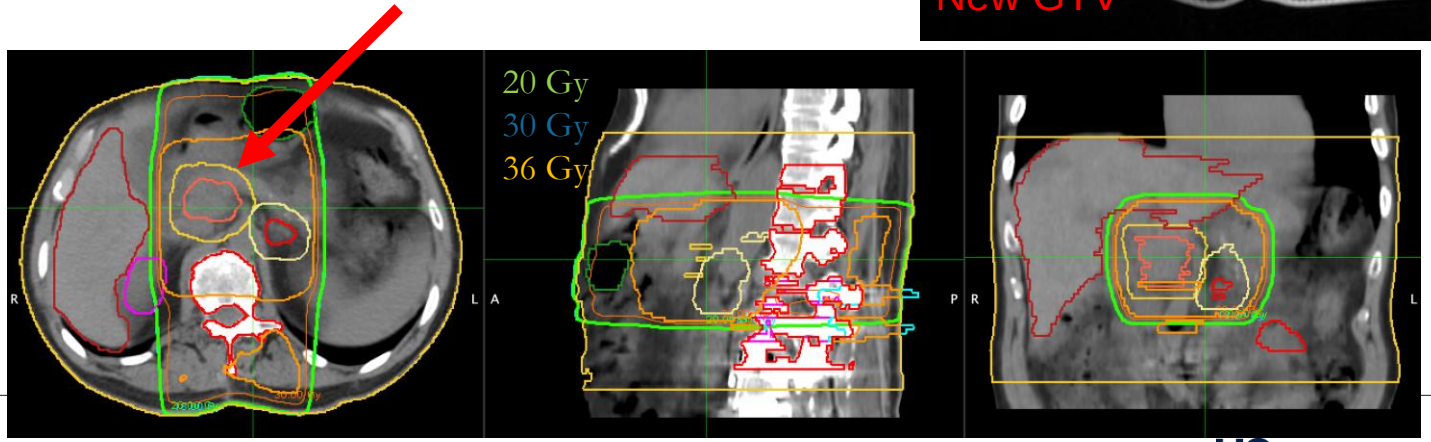
What do you do?

- Obtain his prior treatment plan (ideally full DICOM)
  - Confirm that there is still dose allowed to nearby normal tissues
- Simulation
  - Think about whether positioning will increase separation between target and OAR(s)
  - Think about whether restrictive motion management (e.g. SDX or ABC breath hold) may spare OARs

Review of prior plan

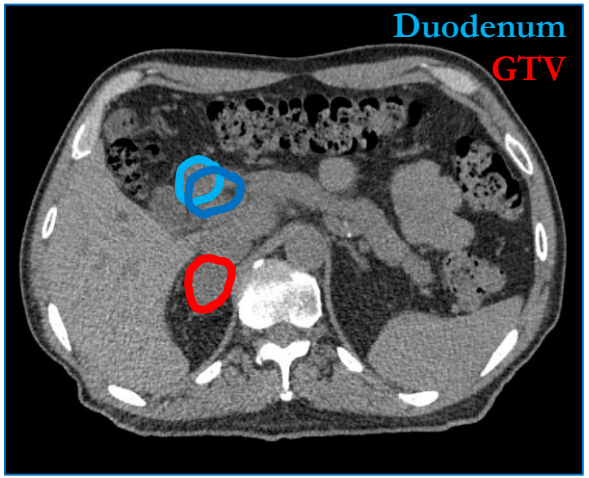
- How close are the old and new targets?
- What normal tissues will be re-treated?





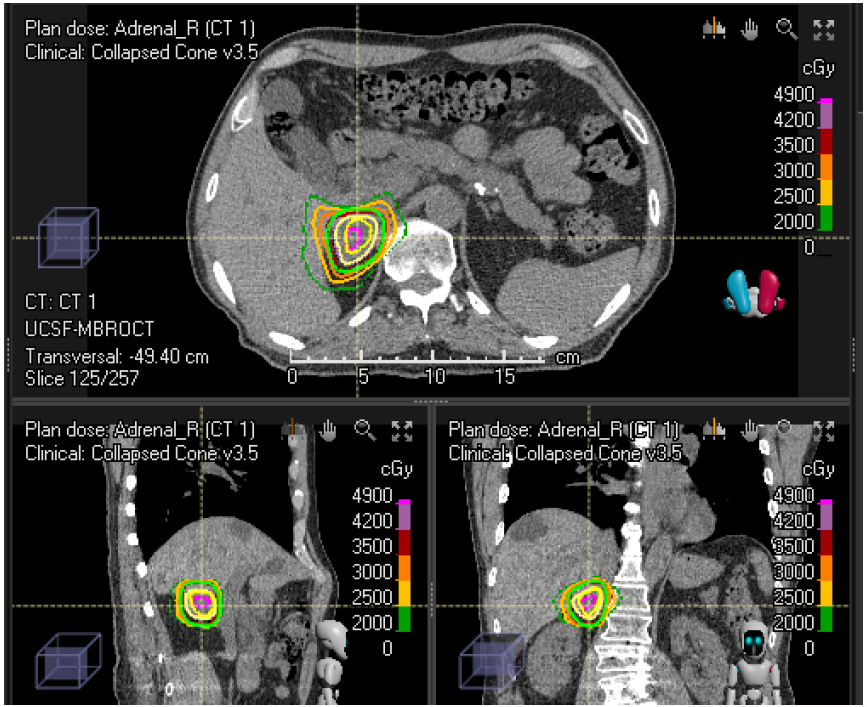
What will you examine in the old plan?

- How much dose did the closest OARs receive before?
- Are these the *same OARs* which will be hit this time?
- Are the same *regions* of those OARs going to be hit this time?
  - include changes in relative geometry



Set planning limits to specific portions of OAR

New plan



- How do you approach a composite?
- Considerations:
  - Quality of image registration
  - Physical vs biologic dose
  - What were the IGRT instructions before?

Double check composite doses including new plan

Several factors which could compromise the accuracy of dose accumulation

SA-CME

- Image registration is not good in the area of interest
- Dose calculation algorithms did not use density corrections
- Plans have different fractionations which was not accounted for

Take composite plans with a grain of salt.

How certain will you be about dose?

- **Uncertainty about current dose:**
  - Variability of overall patient setup
  - Variability of breath holds
  - Variability of relative geometry
- **Uncertainty about prior dose:**
  - Also uncertainty about specific voxels previously radiated
- **Uncertainty about dose limits**

How you bias estimates will depend on clinical scenario

General Scenarios

- 75yof with prior RT for pancreatic cancer is hospitalized with GI bleeding due to tumor invasion

Benefits outweigh the risk

- 45 year old with metastatic colorectal cancer treated with SBRT to a solitary liver metastasis abutting the stomach 3 years ago has a new tumor, also abutting the stomach

Benefits *may* outweigh the risk
-Estimate higher stomach dose to be on the safe side

Dose limits for re-irradiation: What guidance exists?

- **Types of experiences:**
  - Single institution retrospective reviews
  - Multi-institution retrospective reviews
  - Few prospective trials
- **Detailed dosimetry studies:**
  - Sparse
  - Wide error bars

As of 2018, the most comprehensive table for re-RT

Table 2: Recommended/accepted re-irradiation normal tissue tolerances in late reacting tissues

Organ/tissue	Accepted re-irradiation dose-fractionated (Gy)	Accepted re-irradiation dose-stereotactic (Gy)	Accepted time interval between RT courses	Extent of OAR recovery
Soft tissue/ muscle	Doses over 50 Gy conventional EBRT produce better control[16,17]		>12 months	Large scale data not available; only case serie's present
Brain/ brainstem	Cumulative BED not exceed 130-159 Gy with an α/β ratio equal 2 Gy2[18]		>12 months	Partial
	30-40 Gy in fractionated RT[19]	24 Gy for involved volume <20 mm, 18 Gy for volume 21-30 mm and 15 Gy for volume 31-40 mm[6]		
Spinal Cord	cumulative BED should not exceed 130 Gy2[18]		>12 months	Partial
	20-24 Gy in10-12 fractions[13,14]	dose threshold for thecal sac 10 Gy in single fraction and nBED of 30-35 Gy 2/2 for up to five fractions		
Heart	Cumulative dose to the heart (BED_{3Gy}) should not exceed 70 Gy_3 and the point dose (0.1 cc) Dmax not >49 Gy_3[20]		>24 months	Partial
Great vessels	cumulative BED should not exceed 90-100 Gy2[21]		>36 months interval can produce estimated 65% OAR recovery[21]	1%-2% aortic toxicities noted; carotid blowout
Head and neck soft tissues	The dose ranges from 58-60 Gy[22]	18-40 Gy in 3-5 fractions to the 65%-85% isodose line over consecutive days[6]	>6 months-1 year	Lesser volume and more mucosa means more OAR recovery
Mandible	Cumulative dose not defined, but tolerance below 100 Gy_3 without cortical breach			
Parotid	Can tolerate cumulative dose of 45 Gy[23]		>12-18 months	
Optic structures	Re-irradiation constraints limited to <8-10 Gy for 10 cm^3 volume[24]		>12 months	
Urinary bladder	Can tolerate point cumulative doses of up to 120 Gy3[25]		>6 months-1 year	
Pelvic ureter	Can tolerate point cumulative doses of up to 110 Gy3[26]		>24 months	Ureteric stenosis
Rectal mucosa and wall	Total cumulative doses 70-100 Gy with a median total dose of 85 Gy[27,28]	IORT dose of 10-20 Gy[26,28]		Peripheral neuropathy most commonly seen with IORT
Femoral heads	Blood supply to the femoral head is defining point of action. Constraint similar to blood vessels; cumulative BED should not exceed 90-100 Gy2		>2-3 years gap can help recovery	Avascular necrosis of the head is the catastrophic event
Breast soft tissues	40-50 Gy given within 4 days with PDR brachy minimum re-radiation dose in fractionated schedule is 40 Gy		Minimum 6 months	Moderate skin and subcutaneous tissue side effects seen; mainly erythemas and skin telangiectasias
				Expected full OAR recovery

Das, et al.
J Current Oncology 2018

How do we advance?

We need a concerted effort to assess where we are now and collect data to improve our understanding

SEMINARS IN RAD ONC SPECIAL ISSUE?

AAPM TASK GROUP?

ASTRO PRACTICE GUIDELINE?

RE-TREATMENT REGISTRY?

Progress! Special issue of SRO July 2020

- Medical Physics Consult
- Head & Neck
- GBM
- NSCLC
- GI
- GU
- Liver
- Protons

What are the most critical organs at risk?

Serial Organs	Toxicity
Spinal Cord	Paralysis
Blood vessel (Carotid)	Rupture and death
Brain	Brain damage
Bowel	Bowel bleeding/perforation
Parallel Organs	
Lungs	Fibrosis/shortness of breath
Liver	Liver failure
Kidneys	Kidney failure

Spinal Cord: Animal data

Int. J. Radiation Oncology Biol. Phys., Vol. 25, pp. 459–464
Printed in the U.S.A.

0360-3016/93 $6.00 + .00

● *Biology Original Contribution*

THE TOLERANCE OF PRIMATE SPINAL CORD TO RE-IRRADIATION

K. K. ANG, M.D.,* R. E. PRICE, D.V.M.,† L. C. STEPHENS, D.V.M.,† G. L. JIANG, M.D.,*
Y. FENG, M.D.,* T. E. SCHULTHEISS, PH.D.‡§ AND L. J. PETERS, M.D.*

The University of Texas M. D. Anderson Cancer Center

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 4, pp. 1013–1020, 2001

0360-3016/01/$–see front matter

ELSEVIER

PII S0360-3016(01)01599-1

BIOLOGY CONTRIBUTION

EXTENT AND KINETICS OF RECOVERY OF OCCULT SPINAL CORD INJURY

K. KIAN ANG, M.D.,* GUO-LIANG JIANG, M.D.,* YAN FENG, M.D.,* L. CLIFTON STEPHENS, D.V.M.,†
SUSAN L. TUCKER, PH.D.,‡ AND ROGER E. PRICE, D.V.M.†

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Rule of thumb: 50% recovery after 1 year

Caveat: Follow up is limited

Spinal Cord: Human patient data

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 107–116, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.021

CLINICAL INVESTIGATION **Central Nervous System Tumor**

REIRRADIATION HUMAN SPINAL CORD TOLERANCE FOR STEREOTACTIC BODY RADIOTHERAPY

Arjun Sahgal, M.D.,* Lijun Ma, Ph.D.,† Vivian Weinberg, Ph.D.,‡ Iris C. Gibbs, M.D.,§ Sam Chao, M.D.,¶ Ung-Kyu Chang, M.D.,‖ Maria Werner-Wasik, M.D.,** Liliyanna Angelov, M.D.,¶ Eric L. Chang, M.D.,†† Moon-Jun Sohn, M.D.,‡‡ Scott G. Soltys, M.D.,§ Daniel Létourneau, Ph.D.,§§ Sam Ryu, M.D.,¶¶ Peter C. Gerszten, M.D.,‖‖ Jack Fowler, Ph.D.,*** C. Shun Wong,††† and David A. Larson.†

Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
()*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions (30 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions (37.5 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions (42 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions (40 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions (43 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions (50 $Gy_{2/2}$)	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

-5 pts with radiation myelopathy compared with 14 patients without
-All myelopathy pts had 10+ Gy fx

*and the EQD2 does not exceed 70 Gy

Sahgal, et al. *IJROBP* 2012

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Head and Neck

- Re-RT for H&N cancer has a long history
- Multiple society guidelines, even UpToDate chapter
- Severe toxicities include:
  - Carotid blowout (3% risk, 76% fatal)
  - Osteonecrosis
  - Dysphagia
  - Fibrosis

Head and Neck

-8 institutions
-505 pts
-17% Grade 3+ late toxicity

Volume, Dose, and Fractionation Considerations for IMRT-based Reirradiation in Head and Neck Cancer: A Multi-institution Analysis

Jimmy J. Caudell, MD, PhD,* Matthew C. Ward, MD,† Nadeem Riaz, MD, MS,‡ Sara J. Zakem, MD,§ Musaddiq J. Awan, MD,§ Neal E. Dunlap, MD,‖ Derek Isrow, MD, PhD,¶ Comron Hassanzadeh, BS,# John A. Vargo, MD,** Dwight E. Heron, MD, MBA, FACRO, FACR,**,†† Samuel Marcrom, MD,‡‡ Drexell H. Boggs, MD,‡‡ Chandana A. Reddy, MS,† Joshua Dault, MD,§§ James A. Bonner, MD,‡‡ Kristin A. Higgins, MD,‖‖ Jonathan J. Beitler, MD, MBA, FACR, FASTRO,‖‖ Shlomo A. Koyfman, MD,† Mitchell Machtay, MD,§ Min Yao, MD, PhD,§ Andy M. Trotti, MD,* Farzan Siddiqui, MD, PhD,¶ and Nancy Y. Lee, MD‡
on behalf of the Multi-Institution Reirradiation (MIRI) Collaborative

Conclusion

The routine use of elective neck irradiation or hyperfractionation during re-IMRT does not appear beneficial. For patients undergoing definitive re-IMRT, doses of ≥66 Gy appear to be relatively safe and might improve outcomes, especially for high-performing patients or those with a prolonged natural history such as HPV-associated RSP oropharynx cancer. For patients receiving postoperative re-IMRT in the absence of gross disease, doses of 50 to 66 Gy appear adequate.

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Demonstrates the power of collaboration

IJROBP 2018

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Randomized trial!

Original article

Randomized trial comparing two methods of re-irradiation after salvage surgery in head and neck squamous cell carcinoma: Once daily split-course radiotherapy with concomitant chemotherapy or twice daily radiotherapy with cetuximab

Yungan Tao [a], Laura Faivre [a], Anne Laprie [b], Pierre Boisselier [c], Christophe Ferron [d], Guy Michel Jung [e], Séverine Racadot [f], Bernard Gery [g], Caroline Even [a], Ingrid Breuskin [a], Jean Bourhis [h], François Janot [a,*]

[a] *Gustave Roussy Cancer Campus, Villejuif;* [b] *Institut Claudius Regaud, Toulouse;* [c] *Institut du Cancer Val d'Aurelle, Montpellier;* [d] *Centre Hospitalier Universitaire de Nantes;* [e] *Centre Paul Strauss, Strasbourg;* [f] *Centre Léon Berard, Lyon;* [g] *Centre François Baclesse, Caen, France; and* [h] *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

Table 3
Toxicity.

	VP arm	HFR arm
More than 15 days treatment interruption	1/26	0/27
End of reirradiation, 53 patients, grade 3–4	11/26	10/27
6 months from randomization, 50 patients, grade 3–4	7/25	5/25
12 months from randomization, 35 patients, grade 3–4	3/17	5/18
24 months from randomization, 22 patients, grade 3–4	0/8	2/14

Loco-regional recurrences were still the main cause of death in the majority of patients

Radiother Oncol 2018

Brain: Prospective trial

Radiotherapy and Oncology 125 (2017) 223–227

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase I trial

Toxicity and efficacy of re-irradiation of high-grade glioma in a phase I dose- and volume escalation trial

Søren Møller [a,*], Per Munck af Rosenschöld [a], Junia Costa [a,b], Ian Law [b], Hans Skovgaard Poulsen [c,d], Svend Aage Engelholm [a], Silke Engelholm [a,e]

[a] Department of Oncology, Section for Radiotherapy, Rigshospitalet; [b] Department of Clinical Physiology, Nuclear Medicine & PET, Section 3982, Rigshospitalet; [c] Department of Radiation Biology, Section 6321, Rigshospitalet; [d] Department of Oncology, Section 5073, Rigshospitalet; and [e] Department of Oncology, Skåne University Hospital, Lund, Sweden

Table 1
Overview of treatment groups.

	Dose	PTV	EQD_2 tumor	EQD_2 brain
Group 1	3.5 Gy × 10	<100 cm^3	39.4	45.5
Group 2	3.5 Gy × 10 + 7 Gy boost	<100 cm^3	39.4	45.5
			49.7	60.5 (PET pos. volumes)
Group 3	5.9 Gy × 5	<100 cm^3	39.1	52.5
Group 4	3.5 Gy × 10	100–300 cm^3	39.4	45.5

Radiotherapy regimes used in the Re-irradiation study. EQD_2-doses were calculated using the linear-quadratic model and assuming $a/b_{tumor} = 10$ and $a/b_{brain} = 3$. All radiotherapy was given with 5 fractions/week. Abbreviations: PTV (planning target volume), EQD_2 (2-Gy dose equivalent).

Brain: Prospective trial

Table 2
Baseline patient characteristics.

Patients	$n = 31$
Age, years, median (range)	54 (30–74)
Performance status	
0	10 (32%)
1	15 (48%)
2	6 (19%)
Diagnosis	
Glioblastoma	25 (81%)
Glioma WHO gr. III	6 (19%)
Recurrence number	
1	2 (6%)
2	16 (52%)
≥3	13 (42%)
Previous treatment	
Radiotherapy	
60 Gy	26 (84%)
44–45 Gy	4 (13%)
34 Gy	1 (3%)
Temozolomide	31 (100%)
Bevacizumab	20 (65%)
Surgery prior to reirradiation	4 (13%)
Months since diagnosis, median (range)	23 (6–129)
Treatment allocation in study	
Group 1 (3.5 Gy × 10)	12 (39%)
Group 2 (3.5 Gy × 10 + 7 Gy boost)	9 (29%)
Group 3 (5.9 Gy × 5)	5 (16%)
Group 4 (3.5 Gy × 10 to large tumors)	5 (16%)
Target volumes for radiotherapy, median (cm^3)	
Planning target volume	67.0 (16.4–325.0)

- Closed early due to poor accrual
- 31 patients enrolled
- Overall 43% late toxicity
- 3 patients with serious toxicity
  - Radionecrosis at 6 months, resected
  - Balance and fine motor impairment with associated white matter changes
  - Edema requiring hospitalization

Brain prospective trial

Patients: 15 pts

Treatment: Dose escalation 9-11 Gy x 3 fx

Toxicity:

Table 2 Grades 3 and 4 toxicities deemed definitely, possibly, or likely related to study treatment (n = 15)

Toxicity	Grade 3	Grade 4
Fatigue	2	0
Hypertension	1	1
Central nervous system necrosis	1	0
Meningitis	1	0
Leukopenia	1	0
Lymphopenia	1	0
Neutropenia	1	0
Hyponatremia	1	0
Skin infection	1	0
Infections and other infestations	1	0
Muscle weakness	1	0

No grade 5 toxicities were observed.

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Multicenter, Phase 1, Dose Escalation Study of Hypofractionated Stereotactic Radiation Therapy With Bevacizumab for Recurrent Glioblastoma and Anaplastic Astrocytoma

Jennifer Clarke, MD,* Elizabeth Neil, MD,† Robert Terziev, MD,† Philip Gutin, MD,‡ Igor Barani, MD,§ Thomas Kaley, MD,† Andrew B. Lassman, MD,†,‖ Timothy A. Chan, MD,¶ Josh Yamada, MD,¶ Lisa DeAngelis, MD,† Ase Ballangrud, PhD,¶ Robert Young, MD,# Katherine S. Panageas, DrPh,† Kathryn Beal, MD,¶ and Antonio Omuro, MD†

Clarke, et al IJROBP 2017

Practical guidance

Critical Reviews in Oncology / Hematology 126 (2018) 80–91

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Re-irradiation as salvage treatment in recurrent glioblastoma: A comprehensive literature review to provide practical answers to frequently asked questions

Silvia Scoccianti[a,*], Giulio Francolini[a], Giulio Alberto Carta[a], Daniela Greto[a], Beatrice Detti[a], Gabriele Simontacchi[a], Luca Visani[a], Muhammed Baki[a], Linda Poggesi[a], Pierluigi Bonomo[a], Monica Mangoni[a], Isacco Desideri[a], Stefania Pallotta[b], Lorenzo Livi[a]

[a] Radiation Oncology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy
[b] Medical Physics Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy

Table 6
Strategy proposed in the present analysis (to be confirmed in prospective further studies): patients should be stratified according to different disease volume and then, treated with differentiated total dose and fractionation. RS: radiosurgery; HFSRT: hypofractionated stereotactic radiotherapy; CFRT: conventionally fractionated radiotherapy.

Tumor Volume	Technique	EQD2	Example of total dose and number of fractions
≤ 12.5 ml	RS	< 65 Gy	12-15 Gy in a single fraction
> 12.5 ml and < 35 ml	HFSRT	< 50 Gy	25 Gy in 5 fractions
> 35 ml up to 50 ml	CFRT	36 Gy	36 Gy in 20 fractions

Great start. Need agreement and validation

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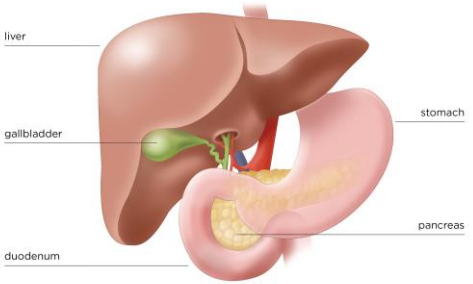
GI structures

- Re-irradiation increasingly being considered for recurrent pancreatic and liver tumors
- With improved chemo, patients are living longer and thus could benefit form additional local therapy
- However, this promise must be balanced against toxicity
  - GI bleed
  - Bowel obstruction
  - Fistula
  - Stenosis

Stomach/small bowel



Advances in Radiation Oncology (2017) 2, 27-36

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Reirradiation with stereotactic body radiation therapy after prior conventional fractionation radiation for locally recurrent pancreatic adenocarcinoma

Amanda J. Koong, Diego A.S. Toesca MD, Rie von Eyben MSc, Erqi L. Pollom MD, Daniel T. Chang MD*

Radiation Oncology Department, Stanford University School of Medicine, Stanford, California

Patients: 23 pts who received prior chemoRT to 30-60Gy

Median followup: 28 months

Treatment: 25 Gy in 1 or 5 fx to recurrence mostly head or tumor bed

Toxicity: Gastric ulcer/fistula in 4 pts, 3 treated with 25 Gyx 1

Stomach/small bowel

Journal of Cancer 2016, Vol. 7 283

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2016; 7(3): 283-288. doi: 10.7150/jca.13295

Research Paper

Stereotactic Body Radiotherapy (SBRT) Reirradiation for Recurrent Pancreas Cancer

Nergiz Dagoglu[1], Mark Callery[2], James Moser[2], Jennifer Tseng[2], Tara Kent[2], Andrea Bullock[3], Rebecca Miksad[3], Joseph D. Mancias[1], Anand Mahadevan[1]✉

1. Department of Radiation Oncology;
2. Department of Surgery;
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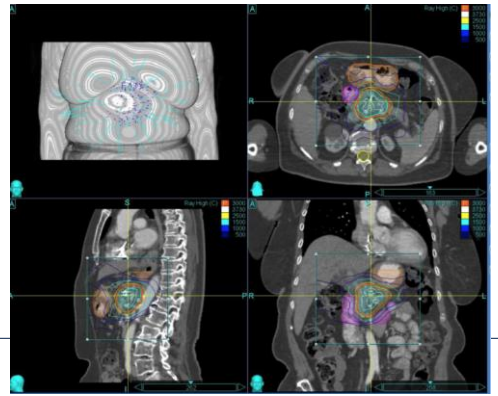


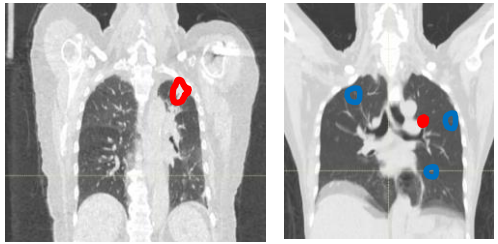
Patients: 30 pts who received prior abdominal RT to 30-60Gy

Median followup: 14 months

Treatment: avg 25 Gy in 3 fx to recurrence, bowel max = rx

Toxicity: 1 GI bleed, 2 bowel obstructions

Lung re-irradiation



- Variety of clinical scenarios for lung re-RT
  - Re-treatment of same site (local advanced NSCLC)
  - First treatment of new site ([oligo]metastases)
- Repeat lung RT must be balanced against toxicity
  - Esophageal toxicity
  - Aortic rupture
  - Bronchial stenosis
  - Pneumonitis/fibrosis

SBRT after fractionated lung RT: pneumonitis

International Journal of Radiation Oncology biology • physics
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Clinical Investigation: Thoracic Cancer

Predicting Radiation Pneumonitis After Stereotactic Ablative Radiation Therapy in Patients Previously Treated With Conventional Thoracic Radiation Therapy

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Patients: 62 pts who received prior thoracic RT

Prior RT: 63 Gy, 21 months earlier

Median followup: 16 months

Treatment: 50 Gy in 4 fx

Toxicity: Pneumonitis in 20%

Table 4 Multivariate binary logistic regression analysis of risk factors for severe RP

Characteristic	*P* value	Relative risk (95% CI)	Beta coefficient	Assigned score
ECOG PS before SABR	.009	10.40 (1.81-59.78)	2.34	1
FEV1 before SABR	.012	12.01 (1.72-84.03)	2.49	1
V_{20} (composite plan)	.021	11.58 (1.45-92.42)	2.45	1
Location of previous PTV	.025	10.79 (1.35-86.44)	2.38	1

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FEV1 = forced expiratory volume in 1 second; PTV = planning target volume; RP = radiation pneumonitis; SABR = stereotactic ablative radiation therapy; V_{20} = percent volume of lung exposed to at least 20 Gy.

Chest wall pain

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

SBRT re-irradiation

Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment

Jeremy M. Kilburn [a,*], Jeffrey G. Kuremsky [a], A. William Blackstock [a], Michael T. Munley [a], William T. Kearns [a], William H. Hinson [a], James F. Lovato [c], Antonius A. Miller [b], William J. Petty [b], James J. Urbanic [a]

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Table 3
Incidence of relevant toxicity in published series of re-irradiation with SBRT.

Toxicity	MDACC series [12]	Karolinska Univ series [13]	Stanford series [14]	Current study
Patients with in-field recurrence or second primary	$n = 11$ n (%)	$n = 29$ n (%)	$n = 15$ n (%)	$n = 33$ n (%)
Chest wall pain requiring narcotics	3 (27)	5 (17)	1 (7)	6 (18)
Pneumonitis				
Grade 2	5 (45)	3 (10)	0	2 (6)
Grade 3	0	1 (3)	0	1 (3)
Esophageal injury				
Esophagitis*	0	0	1 (7)	0
Stricture leading to dilatation	1 (9)	0	0	0
Aorta-esophageal fistula resulting in Grade 5 toxicity	0	0	0	1 (3)†
Vascular injury and death	0	3(10%)	0	1(3)†

Patients: 33 pts who received prior thoracic RT

Fractionated RT: 66 Gy, 18 month interval

Median followup: 17 months

Treatment: 50 Gy in 5 fx

Toxicity: Chest wall pain in 20%

Mortality

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Morbidity of lung SBRT

Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy

Heike Peulen [d], Kristin Karlsson [b,c], Karin Lindberg [a,c], Owe Tullgren [a,c], Pia Baumann [a,c], Ingmar Lax [b], Rolf Lewensohn [a,c], Peter Wersäll [a,c,*]

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Patients: 29 pts who received prior thoracic RT

Prior RT: 15Gy x 2-3 , 14 months earlier

Median followup: 12 months

Treatment: 15Gy x 2-3 most common

Toxicity: 8 pts had grade 3-4 tox, 3 pts (all central) died of massive bleeds at 6 weeks, 4 mo, 11 mo

Aorta limits

Aortic Dose Constraints when Reirradiating Thoracic Tumors

Jaden D. Evans, B.S.[*,†], Daniel R. Gomez, M.D.[*], Arya Amini, M.D.[*], Neal Rebueno, C.M.D.[*], Pamela K. Allen, Ph.D.[*], Mary K. Martel, Ph.D.[‡], Justin M. Rineer, M.D.[§], K. Kian Ang, M.D., Ph.D.[*], Sarah McAvoy, M.D.[*], James D. Cox, M.D.[*], Ritsuko Komaki, M.D.[*], and James W. Welsh, M.D.[*]

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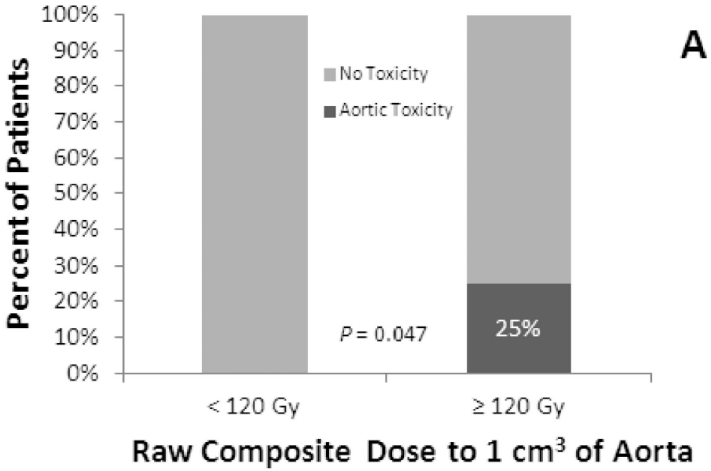


Patients: 35 pts with NSCLC who received 2 courses of RT including the aorta

Prior RT: 30 months earlier

Median followup: 17 months

Treatment: 54-60 Gy, 28-30 Fx

Toxicity: 2 pts had died of massive bleeds, associated with dose to 1cc aorta (120 Gy)

Combined analysis would be helpful

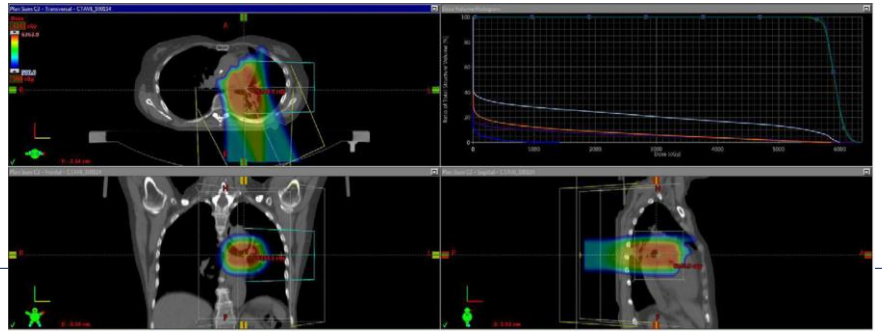
Proton therapy for retreatment: still risky

ORIGINAL ARTICLE

IASLC

Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer

Hann-Hsiang Chao, MD, PhD,[a] Abigail T. Berman, MD, MSCE,[a]
Charles B. Simone II, MD,[a] Christine Ciunci, MD,[b] Peter Gabriel, MD,[a]
Haibo Lin, PhD,[a] Stefan Both, PhD,[c] Corey Langer, MD,[b] Kristi Lelionis, MS,[a]
Ramesh Rengan, MD, PhD,[d] Stephen M. Hahn, MD,[e] Kiran Prabhu, MD,[f]
Marcio Fagundes, MD,[f] William Hartsell, MD,[g] Rosemarie Mick, MS,[h]
John P. Plastaras, MD, PhD[a,*]



Patients: 57 pts who received prior thoracic RT

Prior RT: 19 months earlier

Median followup: 8 months

Treatment: 66.6 Gy

Toxicity: 40% Grade 3+ acute and late toxicity, higher with more central RT

Chao, et al. J Thorac Oncol 2017

UCSF Medical Center

Lung, bronchus, esophagus toxicity

Table 2. Treatment Toxicities and Association with Clinical and Dosimetric Factors

Characteristic	n (%)	*p* Value
Acute grade ≥3 toxicity	22 (39%)	
Treatment factor	Rate of grade ≥3 toxicity	
Central volume overlap		
Low (<41 cm^3)	4 of 28 (14%)	
High (≥41 cm^3)	18 of 28 (64%)	<0.001
Mean heart dose		
Low (<394 cGy)	9 of 34 (26%)	
High (≥394 cGy)	12 of 20 (60%)	0.02
Mean esophagus dose		
Low (<1245 cGy)	7 of 32 (22%)	
High (≥1245 cGy)	14 of 22 (64%)	0.003
Concurrent chemotherapy		
No	3 of 19 (16%)	
Yes	20 of 38 (53%)	0.003

6 deaths	Days after RT
Bronchopulmonary hemorrhage	23
Sepsis	61
Anorexia	86
Pneumonitis	225
Pneumonitis and effusions	170
Tracheoesophageal fistula	211

Chao, et al. J Thorac Oncol 2017

Practical Radiation Oncology (2018) 8, 58-65

practical radiation oncology
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www.practicalradonc.org

IMPT

Basic Original Report

Reirradiation of thoracic cancers with intensity modulated proton therapy

Jennifer C. Ho MD [a], Quynh-Nhu Nguyen MD [a], Heng Li PhD [a], Pamela K. Allen PhD [a], Xiaodong Zhang PhD [b], Zhongxing Liao MD [a], X. Ronald Zhu PhD [b], Daniel Gomez MD [a], Steven H. Lin MD, PhD [a], Michael Gillin PhD [b], Ritsuko Komaki MD [a], Stephen Hahn MD [a], Joe Y. Chang MD, PhD [a,*]

Table 3 Toxicity

Toxicity type	Grade 2 no. (%)	Grade 3 no. (%)
Pulmonary	6 (22)	2 (7)
Esophagitis	7 (26)	0
Dermatitis	2 (7)	0
Fatigue	7 (26)	1 (4)
Pain	7 (26)	0
Hemoptysis	1 (4)	0

Table 4 Composite and re-RT DVH parameters

DVH parameter	Median (range)
Esophagus	
Composite mean (Gy)	30.6 (11.4-49.2)
Composite maximum (Gy)	84.8 (57.1-121)
Composite V_{60} (%)	12.0 (0-15.0)
Re-RT mean (Gy)	9.3 (0.1-38.0)
Re-RT max (Gy)	53.9 (3.1-75.3)
Re-RT V_{60} (%)	0 (0-8.1)
Lungs	
Composite mean (Gy)	14.5 (7-22.5)
Composite V_5 (%)	48.9 (0.4-71.7)
Composite V_{10} (%)	34.7 (0-52.2)
Composite V_{20} (%)	23.8 (0-36.7)
Re-RT mean (Gy)	6.0 (1.8-17.9)
Re-RT V_5 (%)	22.4 (0-45.3)
Re-RT V_{10} (%)	18.7 (0-38.3)
Re-RT V_{20} (%)	13.5 (0-30.9)

DVH, dose-volume histogram; V5, organ volume receiving 5 Gy. Other abbreviations as in Table 1.

Is IMPT better or is this retrospective vs. prospective?

Ho, et al. *PRO 2018*

UCSF Medical Center

ACR Guidelines on Re-RT for NSCLC (in progress)

- Esophagus V60 < 40%, Dmax <100-110 Gy
- Lung V20 < 40%
- Heart mean dose ALARA and V40 < 50%
- Aorta and Great Vessels Dmax < 120 Gy
- Trachea and proximal bronchial tree Dmax <110 Gy
- Spinal Cord Dmax < 57 Gy
- Brachial Plexus Dmax <85 Gy

**In 2 Gy fractions

Summary

- Re-irradiation is increasingly common in everyday practice
- Data on safety of re-irradiation is sparse
- Must consider error bars and clinical scenario
- Must develop standard workflows
  - Improved efficiency: not re-inventing the wheel each time
  - Improved safety: not developing dose limits in a rush

Work to be done

- Must comprehensively collect and analyze data to improve our understanding
- Must devise easily consumable and actionable guidelines
- Must continue the feedback loop to refine our knowledge and guidelines

Whew! We're done! Thanks for hanging around!

Graduation, 2020 style

No ziplining at Whistler after AAPM this time!

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