SBRT alone or with Immunotherapy

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Rome, IT

Research in the department of Radiation Oncology

Immuno-RT
Hypo, SBRT
Oligorecurrent
Particles
Imaging,
Radiomics
Side Effects, QoL

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Immuno-RT

Hypo, SBRT

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Particles

Imaging,

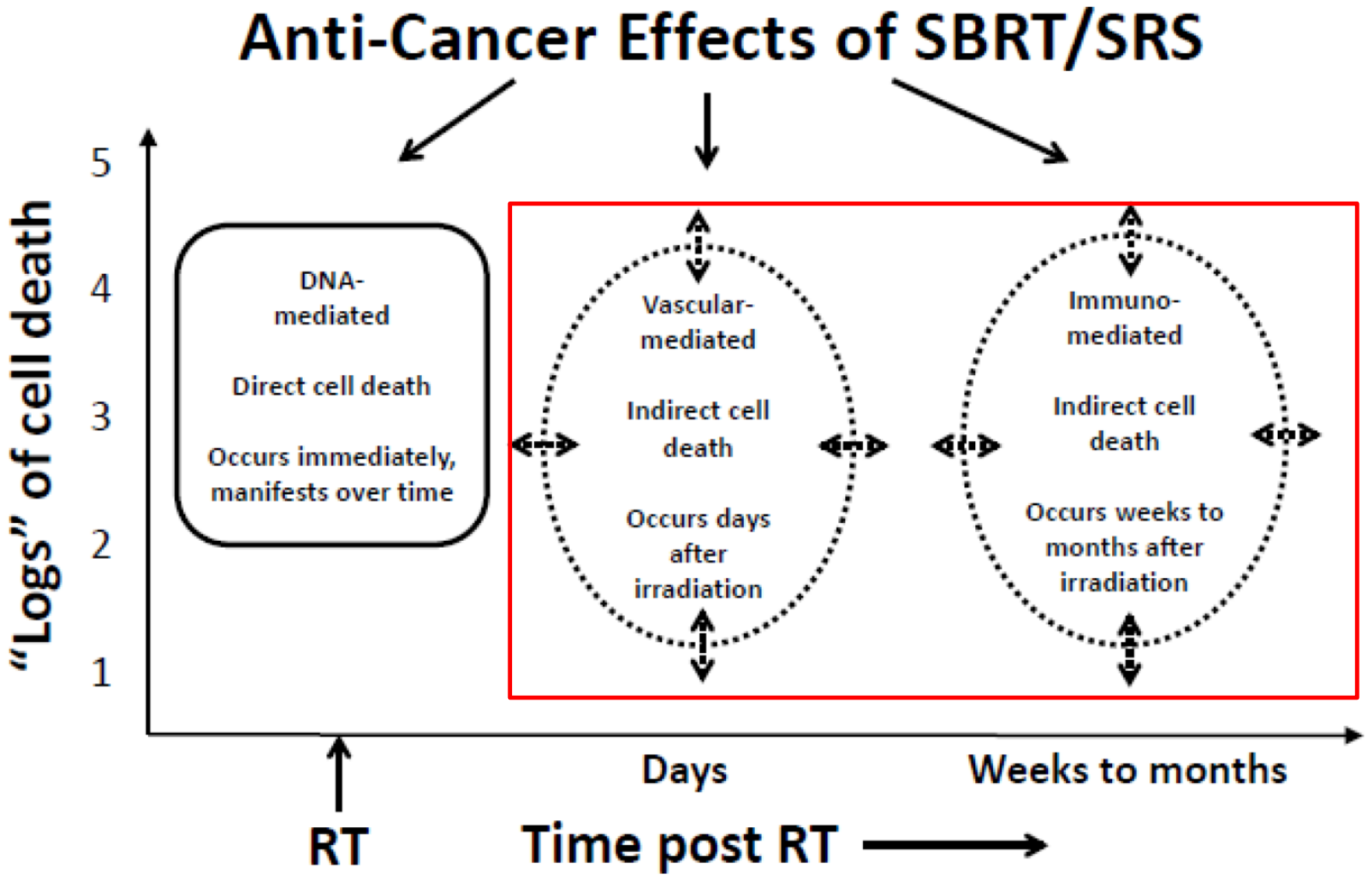
Radiomics

Side Effects, QoL

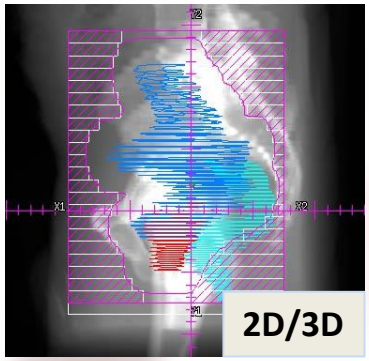
Stereotactic Body RadioTherapy - Definition

The American Society for Radiation Oncology (ASTRO) & the American Society of Clinical Oncology (ASCO) define ultrahypofractionated (UHF) radiotherapy as doses per treatment of 5.0 Gy/day or higher (Morgan et al, JCO 2018)

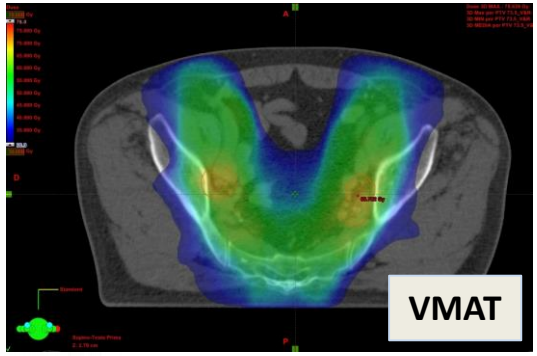
- d>5 Gy
- < 10 fxs
- only GTV
- intensity modulation


Anti-Cancer Effects of SBRT/SRS
"Logs" of cell death
5
4
3
2
1
DNA-mediated
Direct cell death
Occurs immediately, manifests over time
Vascular-mediated
Indirect cell death
Occurs days after irradiation
Immuno-mediated
Indirect cell death
Occurs weeks to months after irradiation
Days
Weeks to months
RT
Time post RT

Development of RT



Large volumes



1895	1919	1951	1953	1972	1980	1986	1994	2000	2010
Discovery of x-rays	Discovery of the proton	Cobalt Unit	LINAC	CT	3D planning	MLC	IMRT	IGRT	ability to deliver dose precisely and accurately to a region of interest in the patient

1896 First pt treated w x-rays

1954 First pt treated w protons

2DRT

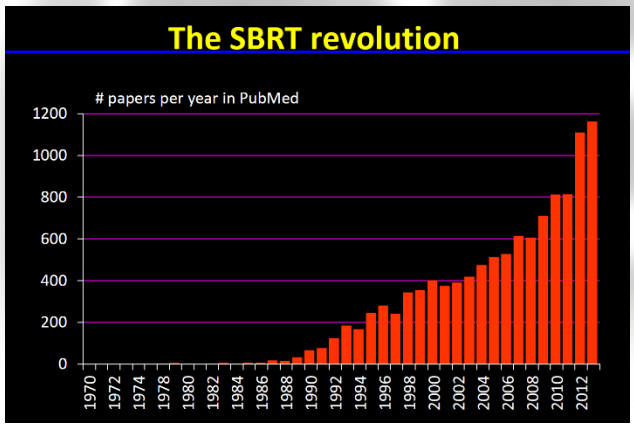
3DCRT

IMRT

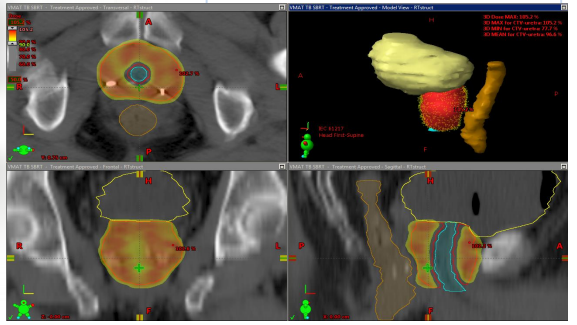
IGRT

VMAT

SBRT



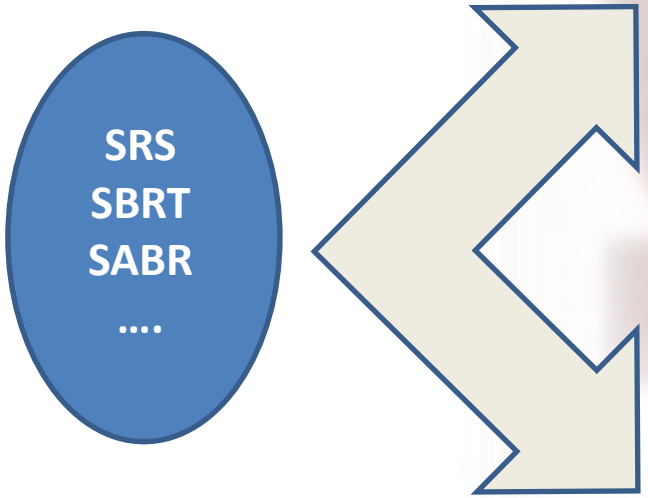
SMALL volumes



DEFINITIVE, RADICAL, CURATIVE…. Setting

i.e. LR/IR PCA, early stage lung, …

…as an alternative to Surgery



PALLIATIVE, METASTATIC…. Setting

i.e. oligo- RCC, melanoma, lung …

to quickly/effectively address M diz….

… to delay systemic tmt/switch

… to consolidate response to systemic

… to enhance response to IT (abscopal)

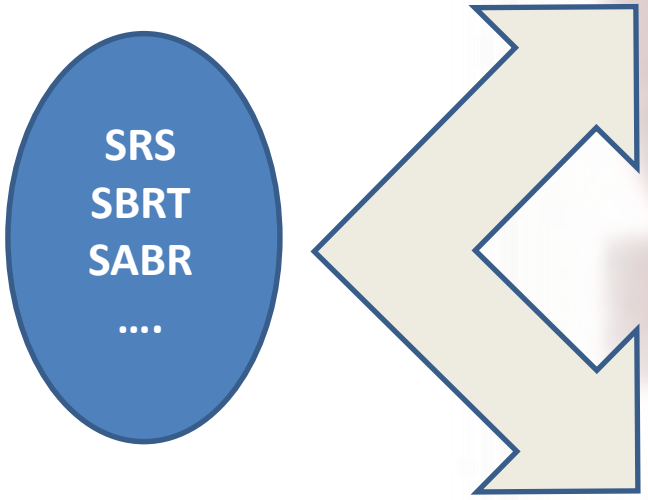
DEFINITIVE, RADICAL, CURATIVE…. Setting

i.e. LR/IR PCA, early stage lung, …

…as an alternative to Surgery

SBRT in 3 fxs for LR PCA

SBRT in 3 fxs for early stage glottic ca



PALLIATIVE, METASTATIC…. Setting

i.e. oligo- RCC, melanoma, lung …

to quickly/effectively address M diz….

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… to consolidate response to systemic

… to enhance response to IT (abscopal)

SBRT & IT for early stage NSCLC

SBRT in 3 fxs for LR/fav-IR PCa

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Table 1: Regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very Low[a]	Low[a]	Favorable or Good Prognostic[b] Intermediate	Unfavorable, or Poor Prognostic[b], Intermediate	High and Very High[c]	Node Positive
Beam Therapies						
72–80 Gy at 2 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5–3 y ADT	✓ with ADT
75.6–81.0 Gy at 1.8 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5–3 y ADT	✓ with ADT
70.2 Gy at 2.7 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5–3 y ADT	✓ with ADT
70 Gy at 2.5 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5–3 y ADT	✓ with ADT
60 Gy at 3 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5–3 y ADT	✓ with ADT
51.6 Gy at 4.3 Gy per fraction	✓	✓	✓			
37 Gy at 7.4 Gy per fraction	✓	✓	✓			
40 Gy at 8 Gy per fraction	✓	✓	✓			
36.25 Gy at 7.25 Gy per fraction	✓	✓	✓			
Brachytherapy Monotherapy						
Iodine 125 implant at 145 Gy	✓	✓	✓			
Palladium 103 implant at 125 Gy	✓	✓	✓			
Cesium implant at 115 Gy	✓	✓	✓			
HDR 27 Gy at 13.5 Gy in 2 implants	✓	✓	✓			
HDR 38 Gy at 9.5 Gy BID in 2 implants	✓	✓	✓			
Combined EBRT and Brachytherapy (EBRT 45–50.4 Gy at 1.8–2.0 Gy/fx, unless otherwise noted)						
Iodine 125 implant at 110–115 Gy				✓ ± 4 mo ADT	✓ with 1–3 y ADT	
Palladium 103 implant at 90–100 Gy				✓ ± 4 mo ADT	✓ with 1–3 y ADT	
Cesium implant at 85 Gy				✓ ± 4 mo ADT	✓ with 1–3 y ADT	
HDR 21.5 Gy at 10.75 Gy x 2				✓ ± 4 mo ADT	✓ with 1–3 y ADT	
EBRT 37.5 Gy at 2.5 Gy + 12–15 Gy single HDR				✓ ± 4 mo ADT	✓ with 1–3 y ADT	

SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise.

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Prostate Cancer

NCCN Guidelines Index
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PRINCIPLES OF RADIATION THERAPY

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

√ indicates an appropriate regimen option if radiation therapy is given. See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-9, PROS-13, and PROS-G for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High[c]	Regional N1	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR Iodine 125 Palladium 103 Cesium	145 Gy 125 Gy 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125 Palladium 103 Cesium	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x1 fx 10.75 Gy x 2 fx			✓	✓		

SBRT - Evidence

Trial	To Be Accured	Population	Endpoint	Dose Arms
HEAT NCT 01794403	456	Low and Int Risk	PSA-RFS NON-INFERIORITY	36.25 Gy/5 fx vs 70.2Gy/26 fx
HYPO-RT-PC ISRCTN45905321	1200	Int and High Risk	PSA-RFS NON-INFERIORITY	42.7 Gy/7 fx vs 78 Gy/39 fx
NRG-GU005	606	Intermediate Risk	QOL SUPERIORITY	36.25 Gy/5 fx vs 70Gy/28fx
PACE B NCT01584258	858	Low and Int Risk	PSA RFS NON-INFERIORITY	36.25 Gy/5 fx vs 78 Gy/39 fx

Open issues:

- PT SELECTION (LR vs IR vs HR)
- # fxs per week
- D/# fxs (1-8)
- Dose distribution (homo vs hetero)
- Role of Androgen Deprivation

Clinical Investigation

International Journal of Radiation Oncology biology • physics

Five-Year Outcomes of a Phase 1 Dose-Escalation Study Using Stereotactic Body Radiosurgery for Patients With Low-Risk and Intermediate-Risk Prostate Cancer

Michael J. Zelefsky, MD,* Marisa Kollmeier, MD,* Sean McBride, MD,* Melissa Varghese, BA,* Borys Mychalczak, MD, Richard Gewanter, MD,* Madhur K. Garg, MD,§ Laura Happersett, MS,† Debra A. Goldman, MS,‡ Isaac Pei, PhD,* Mary Lin, BA,* Zhigang Zhang, PhD,‡ and Brett W. Cox, MD‖

*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; †Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York; ‡Department of Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, New York; §Department of Radiation Oncology, Montefiore Medical Center, Bronx, New York; and ‖Department of Radiation Medicine, Northwell Health, Lenox Hill Hospital, New York, New York

Received Oct 4, 2018. Accepted for publication Dec 26, 2018.

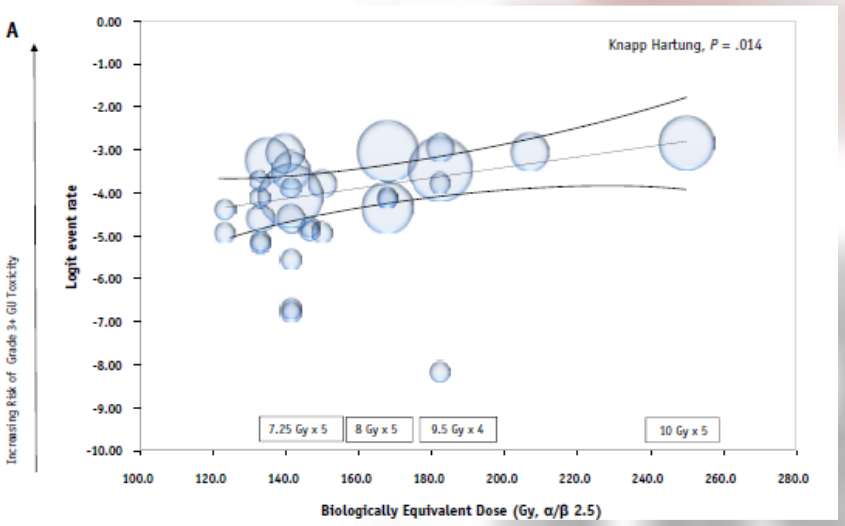
d	n	D	# pts	bFAIL	2-yr pos bx
6.5 Gy	5	32.5 Gy	30	15%	47.6%
7.0 Gy	5	35.0 Gy	35	6%	19.2%
7.5 Gy	5	37.5 Gy	36	0%	16.7%
8.0 Gy	5	40.0 Gy	35	0%	7.7%

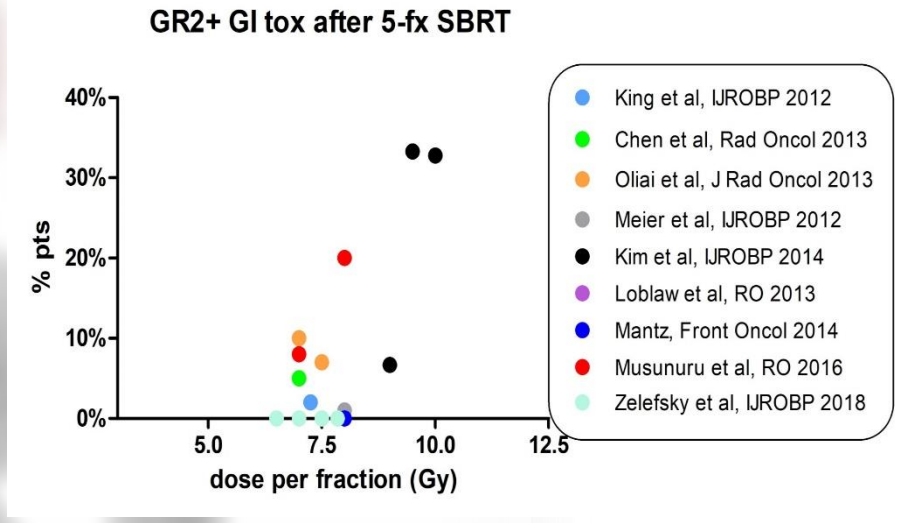
Every other day; CTV to PTV 5 mm (except post); Calipso

Dose/response detected

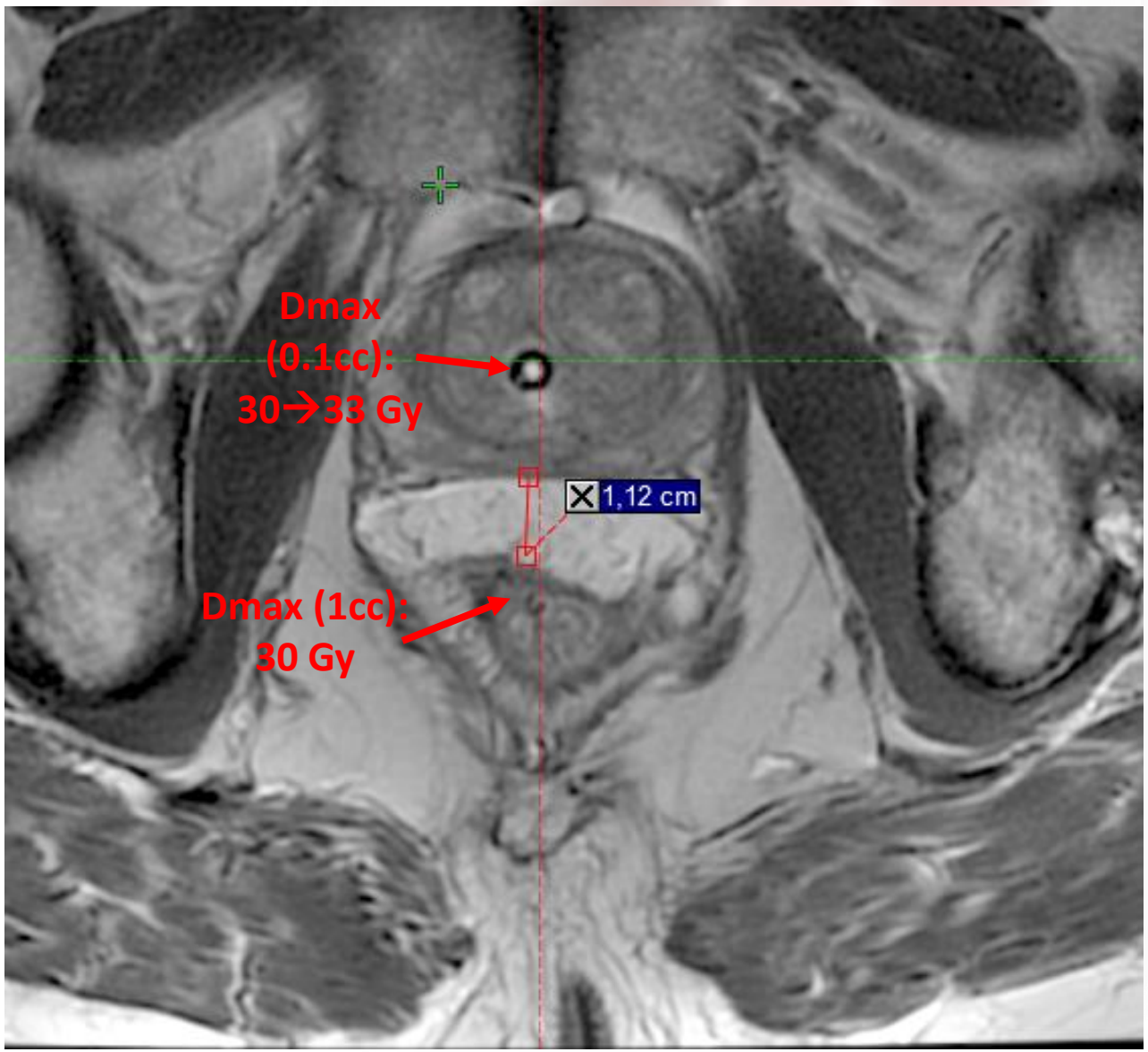
SBRT - Evidence

- There was a significant association with increasing dose (BED2.5) and late grade 3 GU toxicity (p=0.014)





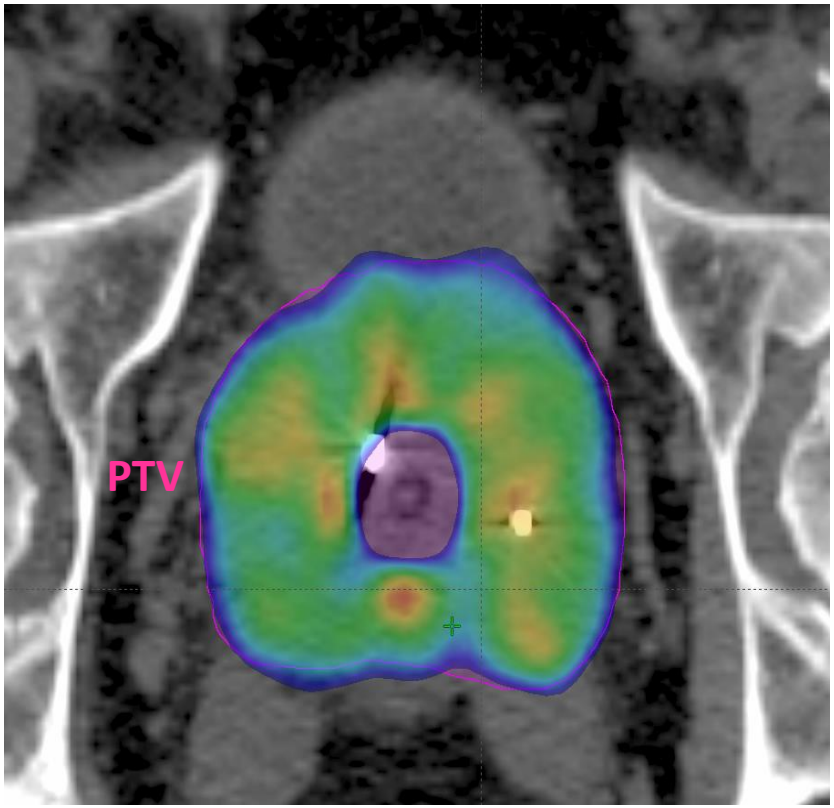
Jackson et al, IJROBP 2019

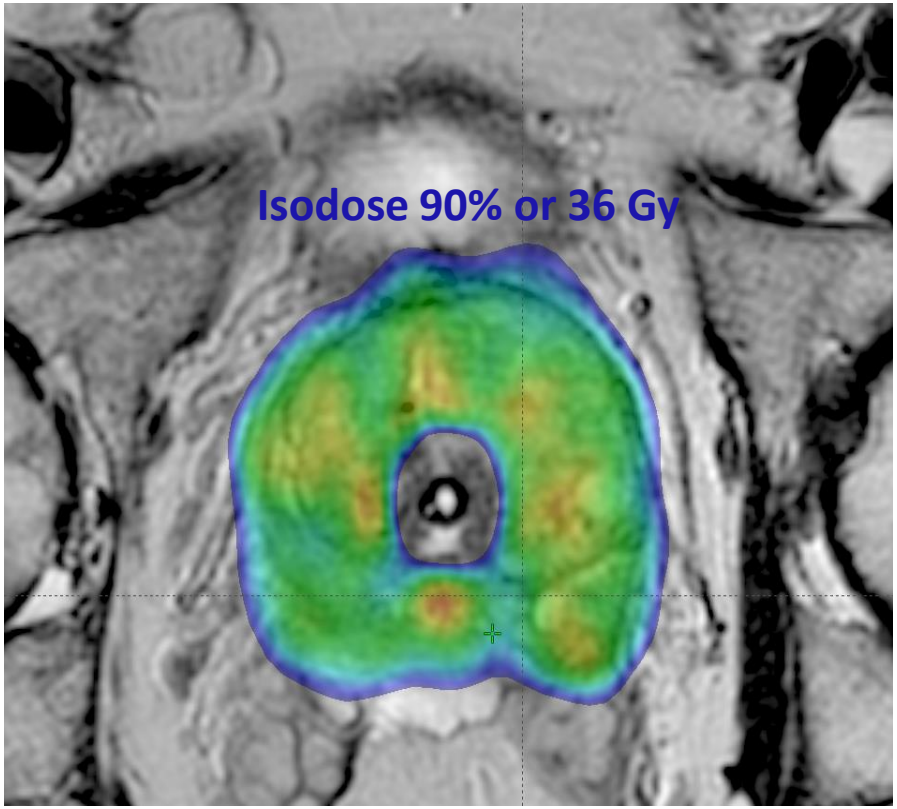


Coverage goals:

PTV-urethra
D93≥36 Gy

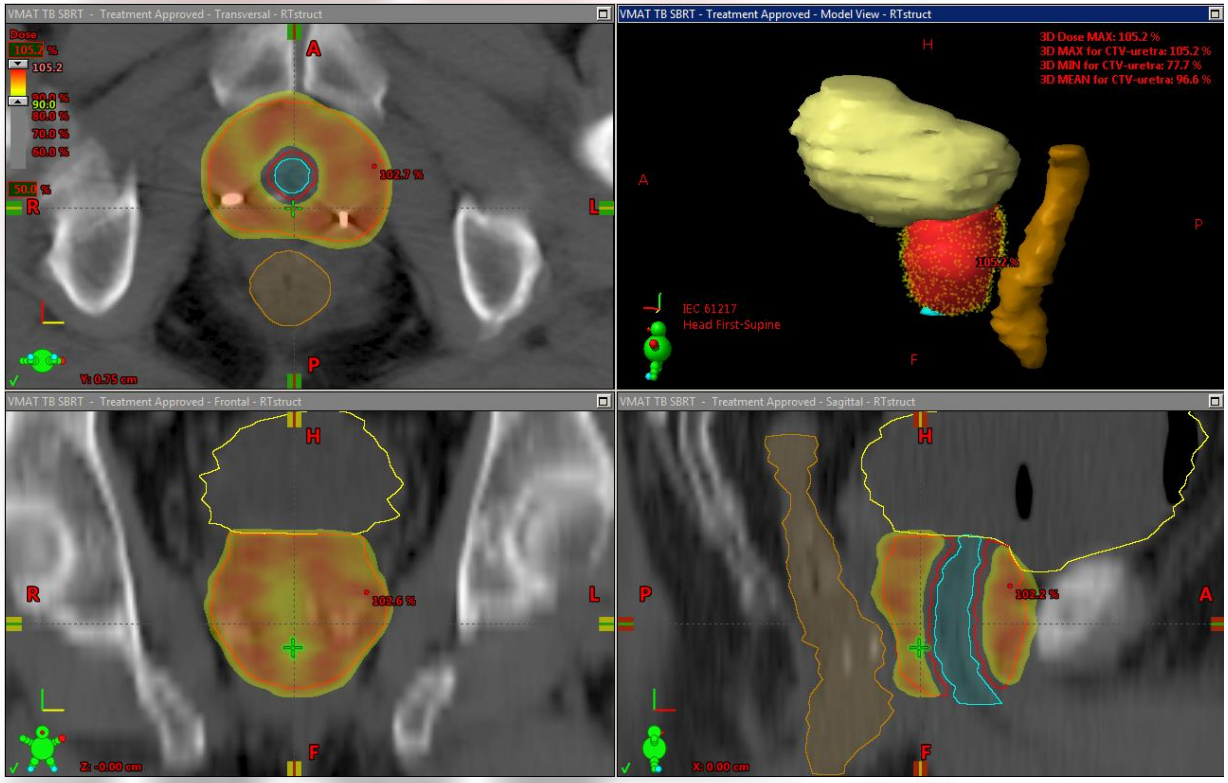
CTV-urethra
D95≥36 Gy


PTV


Isodose 90% or 36 Gy

SBRT protocol

- Low and fav int risk PCA
- mpMR (no ECE)
- **Spacer**, fiducials
- plMR, urinary catheter
- Target: prostate
- OAR: rectum, urethra (+2 mm), bladder neck…
- CTV to PTV exp: 4 mm
- Px: 40 Gy / 3 fxs



SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA SAN GIOVANNI ADDOLORATA
azienda sanitaria universitaria integrata di udine
IRE

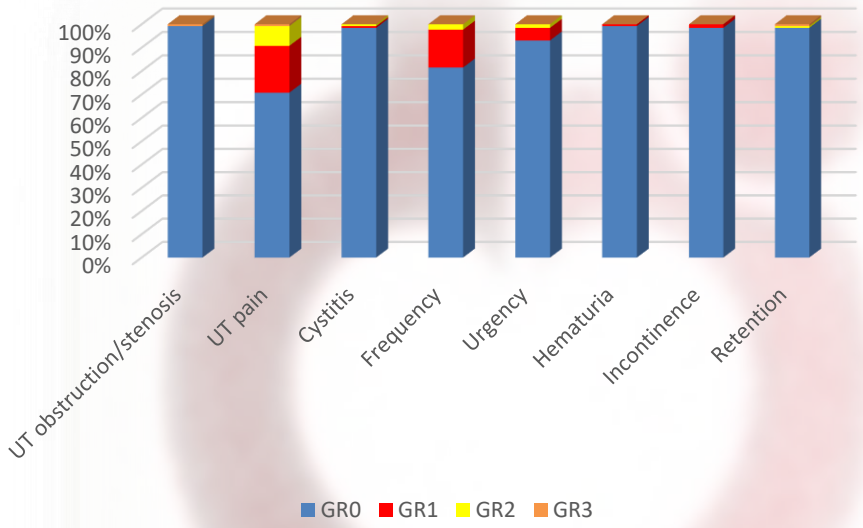
PHASE I part: prevalence of GU GR2+ tox @ 1 yr <15%

PHASE I part: prevalence of GU GR2+ tox @ 1 yr <15%

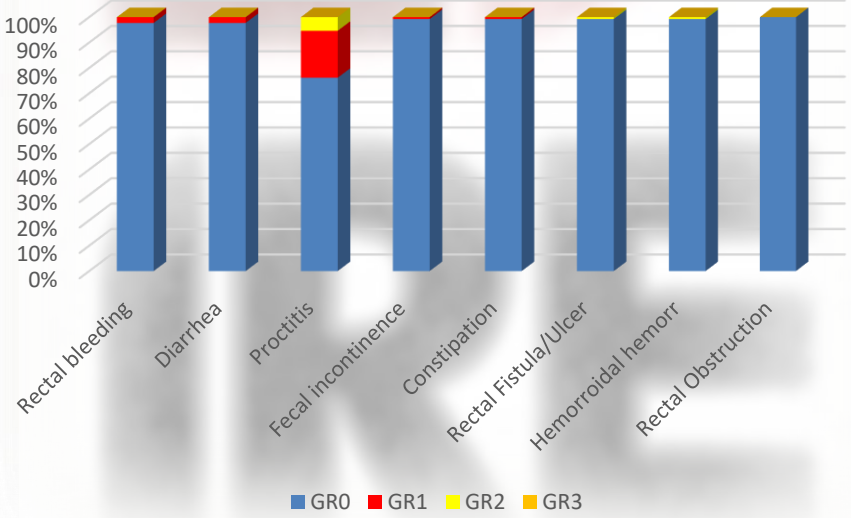
Target/accrued: 59 pts

Characteristic	Strata	Median/#	IQR/%
Age (yrs)		73	68-75.5
GGG	1	42	71.2%
	2	17	28.8%
T stage	1	26	44.1%
	2	33	55.9%
PSA (ng/ml)		7.0	5.0-8.9
Prostate volume (cc)		45	35.5-62.5
Androgen Deprivation	No	55	93.2%
	Yes	4	6.8%
IPSS		7	2-10

Incidence of ACUTE GU tox

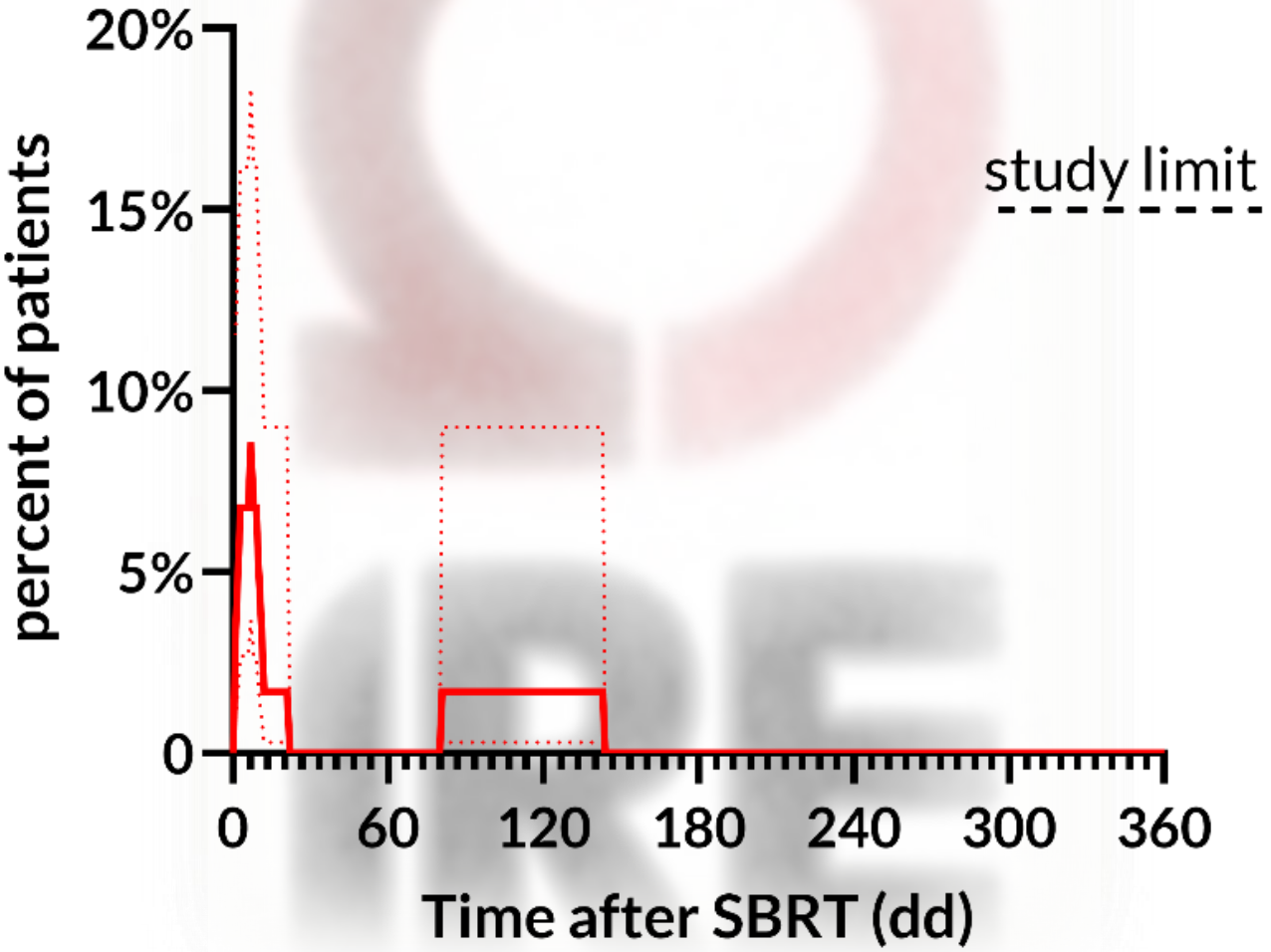


Incidence of ACUTE GI tox



59 pts

Prevalence of GR2+ GU tox



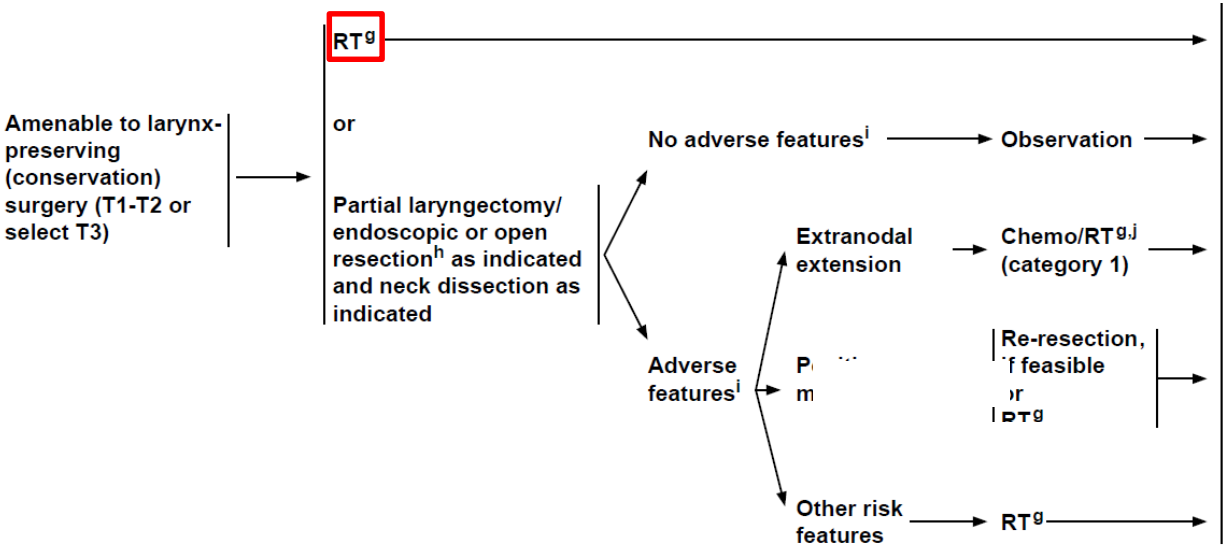
Conclusions

SBRT to 40 Gy in 3 fxs is feasible….

…accrual of phase II is almost completed

SBRT in 3 fxs for early glottic ca

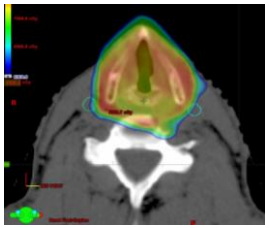
Cancer of the Glottic Larynx



Expect:
85-90% local control rate

Volume: Larynx
Doses:
T1:63 Gy@2.25 Gy or 66 Gy@2 Gy
Tech: 3DCRT or IMRT

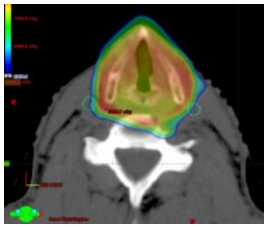
IMRT



Less (high) dose to surrounding tissues (carotids)

Management of Early Stage Glottic Cancer

IMRT



Less (high) dose to surrounding tissues (carotids)

STANDARD OF CARE

RESEARCH

Single Cord (or GTV) Irradiation → **Extreme HYPO**

To allow ext HYPO

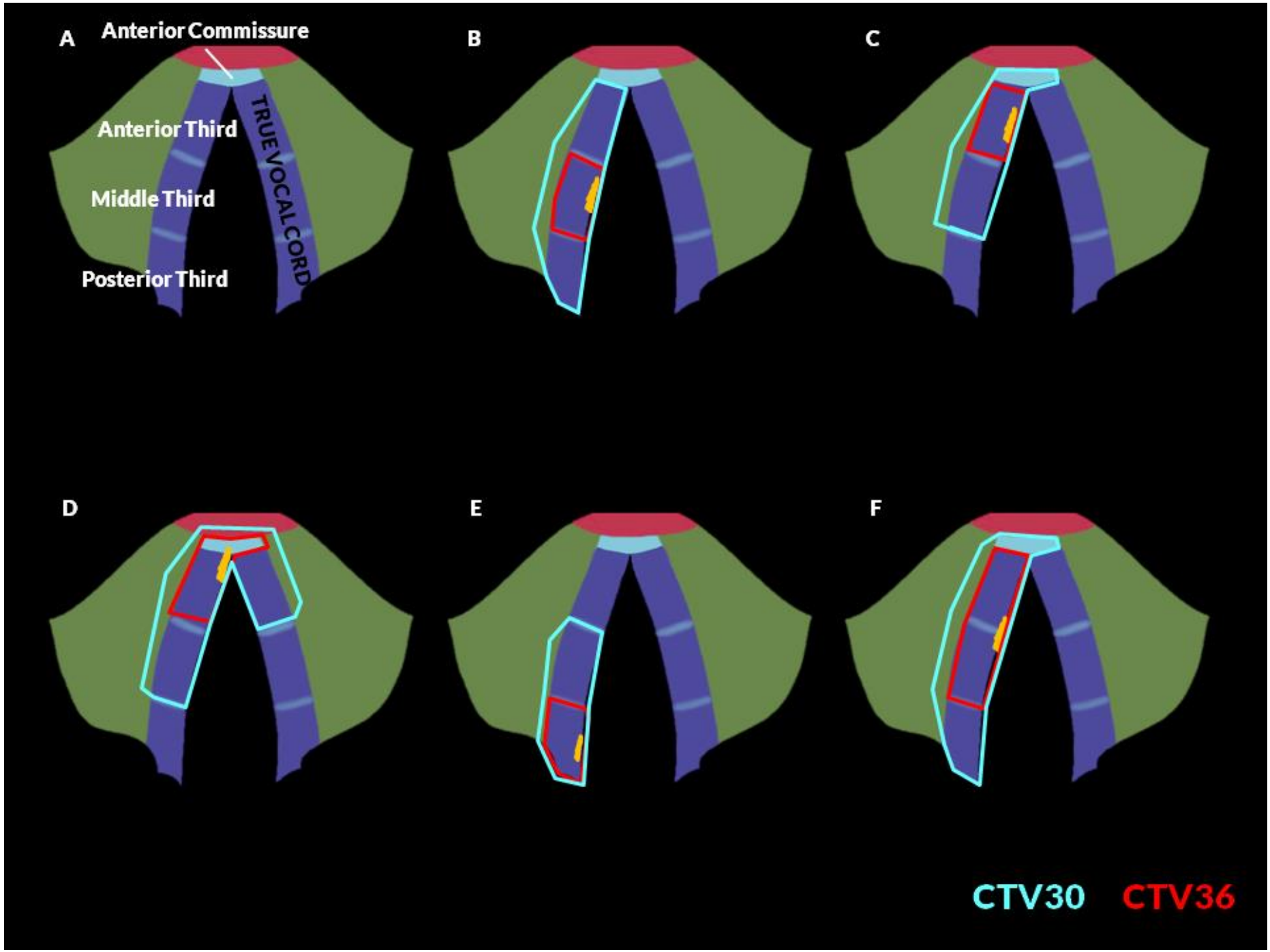
To cut # tmt sessions

d x n	D over t	T stage	EQ D (α/β=3)	Volume	Institution
2 Gy x 35 fxs	70 Gy over 7 wks	T1-2	ref	Whole Larynx	SOC
2.25 Gy x 29 fxs	65.25 Gy over 6 wks	T2	≈69 Gy	Whole Larynx	SOC
2.75 Gy x 20 fxs	55 Gy over 4 wks	T1-2	≈63 Gy	Whole Larynx	James's Institute of Oncology
3.28 Gy x 16 fxs	52.5 Gy over ≈3 wks	T2	≈66 Gy	Whole Larynx	Christie NHS Foundation Trust
3.33 Gy x 15 fxs	50 Gy over 3 wks	T1-2	≈63 Gy	SC or GTV	UT Southwestern, Dallas
3.63 Gy x 16 fxs	58.1 Gy over ≈3 wks	T1a	≈77 Gy	SC	Erasmus, Rotterdam
3.5/2.8 Gy x 17 fxs	59.5/47.6 Gy in 3.5 wks	T1-2	≈77 Gy	GTV/larynx	Soul Univerisity, Korea
4.5 Gy x 10 fxs	45 Gy over 2 wks	T1-2	≈67 Gy	SC or GTV	UT Southwestern, Dallas
5/3.7 Gy x 11 fxs	55/40.7 Gy in ≈2 wks	T1-2	≈88 Gy	GTV/larynx	Soul Univerisity, Korea
8.5 Gy x 5 fxs	42.5 Gy over 1 wk	T1-2	≈98 Gy	SC or GTV	UT Southwestern, Dallas
12/10 Gy x 3 fxs	36/30 Gy over 1 wk	T1	108 Gy	SC	IRCCS Regina Elena, Rome

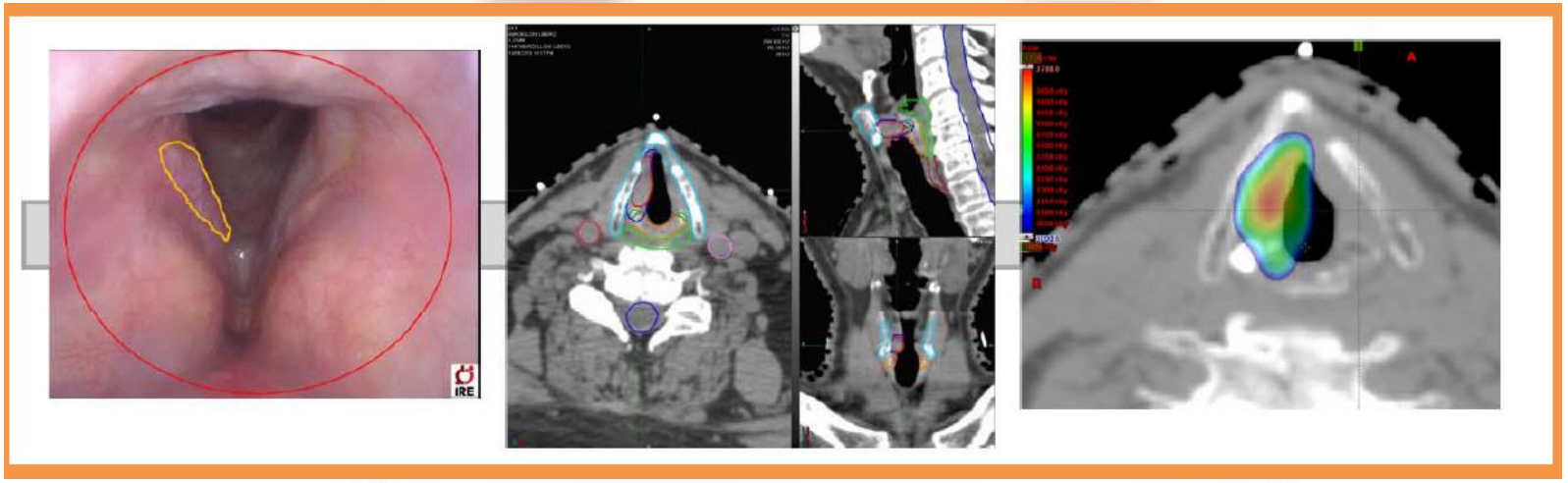
BED: Biological Equivalent Dose
GTV: Gross Tumor Volume

↑ BIOLOGICAL DOSE TO LATE RESP (cartilage) TS

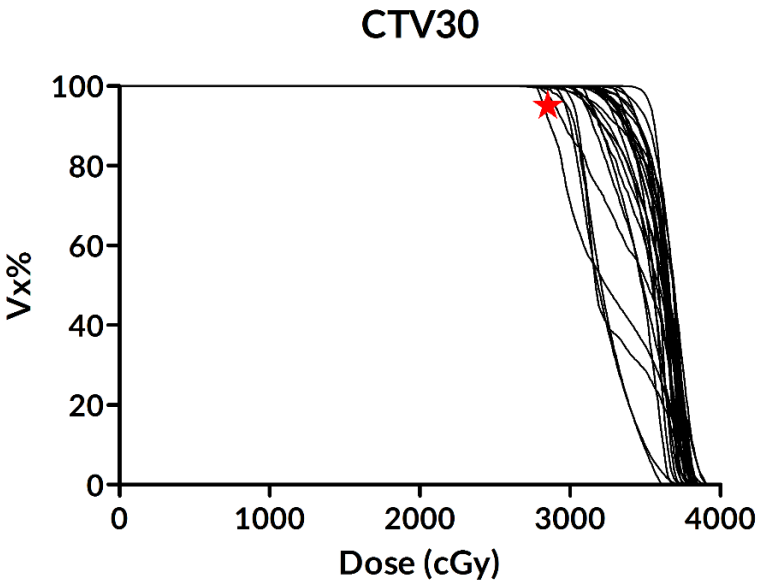
IRE

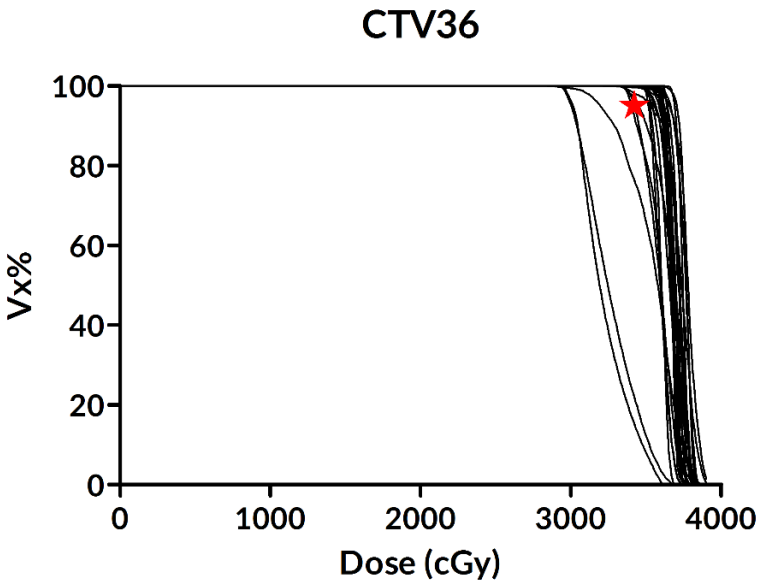

A
Anterior Commissure
Anterior Third
Middle Third
Posterior Third
TRUE VOCAL CORD
B
C
D
E
F
CTV30
CTV36

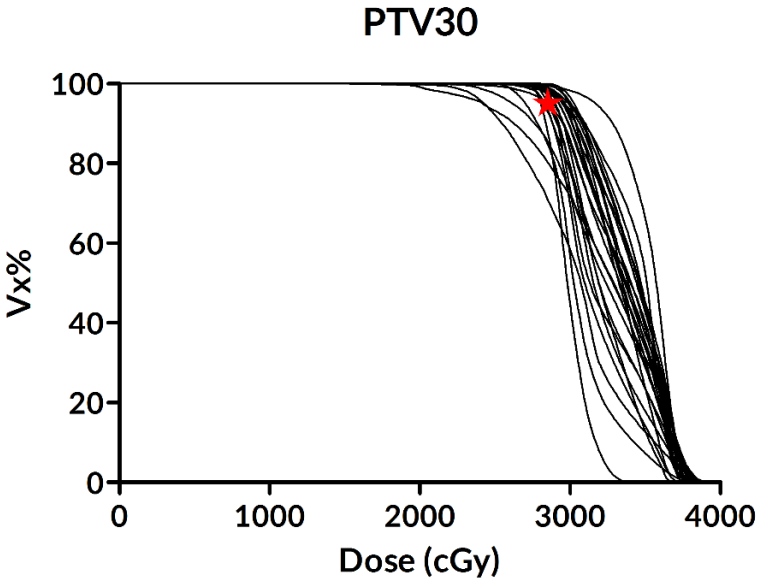
DOSIMETRIC & PRELIMINARY RESULTS IN 27 CONSECUTIVE PATIENTS

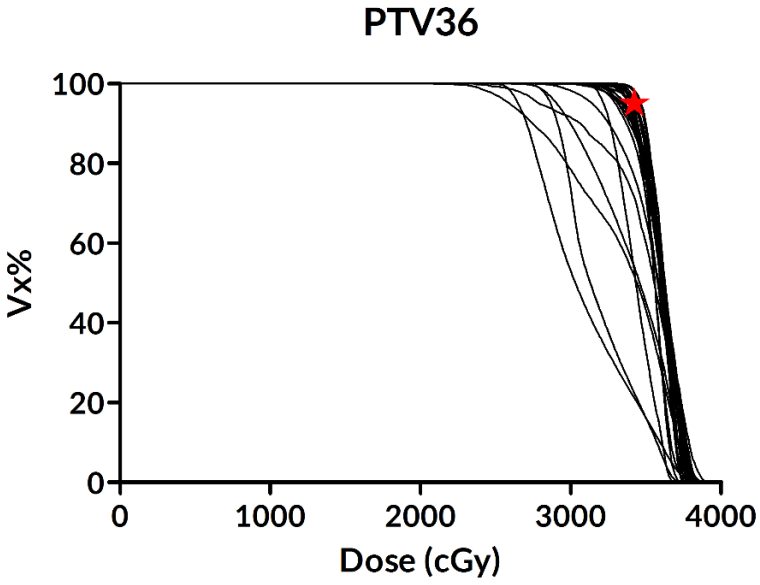


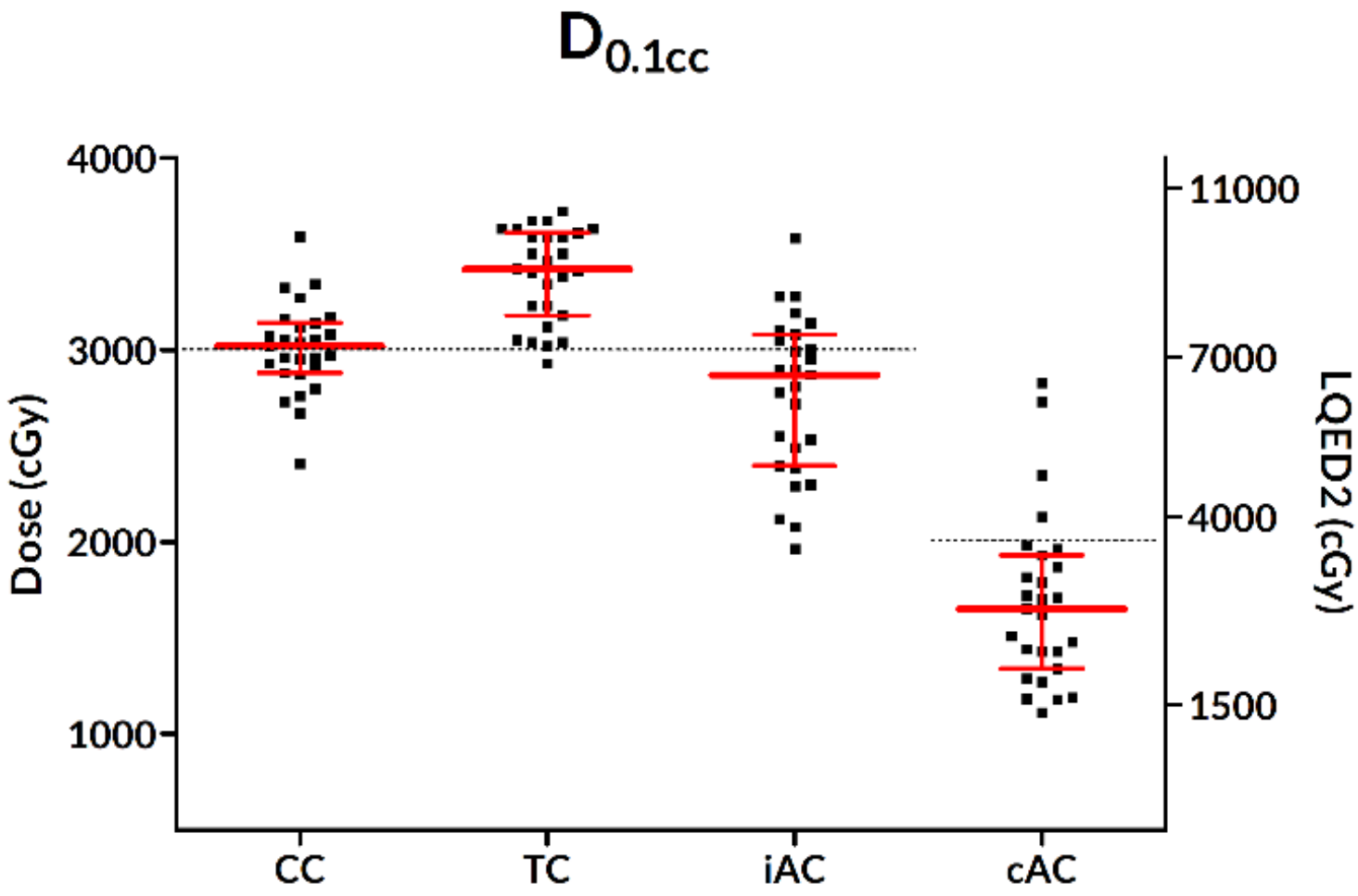
Median follow up of 17.2 months (IQR: 10.2-23.7 mths)


CTV30
100
80
60
40
20
0
Vx%
0
1000
2000
3000
4000
Dose (cGy)

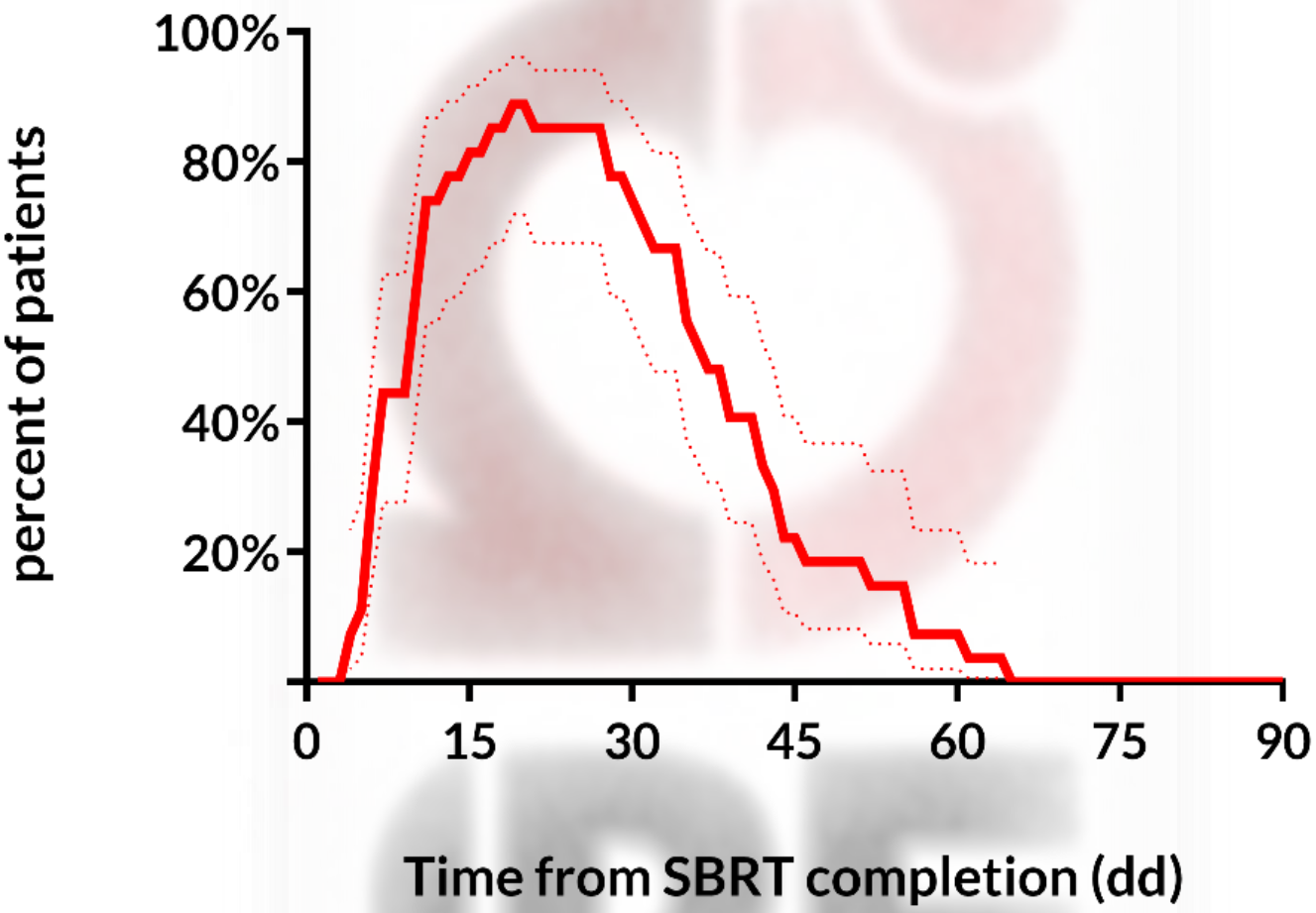

CTV36
100
80
60
40
20
0
Vx%
0
1000
2000
3000
4000
Dose (cGy)


PTV30
100
80
60
40
20
0
Vx%
0
1000
2000
3000
4000
Dose (cGy)

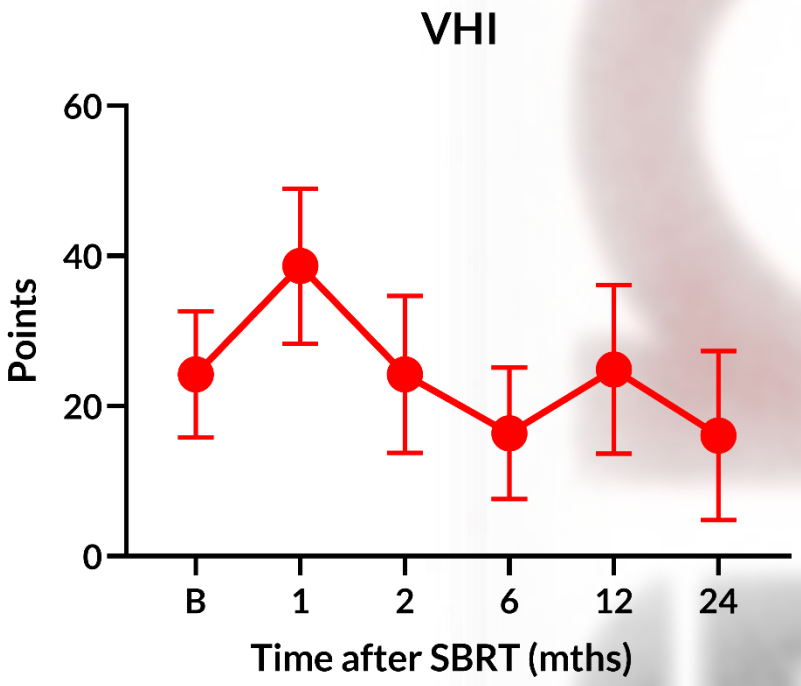

PTV36
100
80
60
40
20
0
Vx%
0
1000
2000
3000
4000
Dose (cGy)

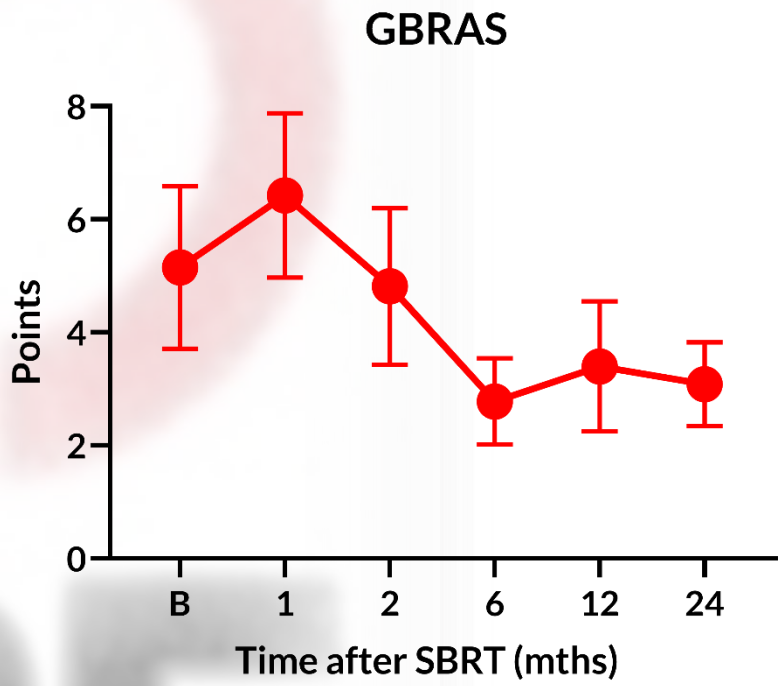

D0.1cc
4000
3000
2000
1000
Dose (cGy)
11000
7000
4000
1500
LQED2 (cGy)
CC
TC
iAC
cAC

PREVALENCE of Any CTCAE GR2+ tox



At 30 days after SBRT 74.1% (55.3-86.8%) of patients had GR2 toxicity.
Acute toxicity resolved after a median time of 38 days (33.3-43.5) from the end of treatment.





Median follow up of 17.2 months (IQR: 10.2-23.7 mths)

- At a median follow up of 17.2 months (IQR: 10.2-23.7 mths) all patients are without evidence of disease;
- 1 pt had chondronecrosis of the iAE, which resolved after conservative S

- 1 pt had soft tissue necrosis with cartilage exposure that resolved after medical therapy

Conclusions

- SBRT to 36 Gy in 3 fxs is dosimetrically challenging
- Acute toxicity is mild
- Preliminary functional & oncologic outcomes are encouraging

SBRT & IT for early NSCLC

EARLY STAGE NSCLC

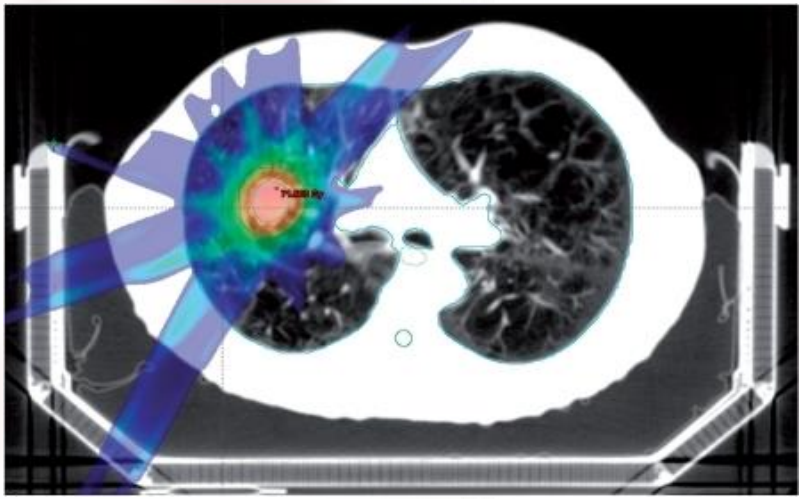
Chest

Volume 124, Issue 5, November 2003, Pages 1946-1955

Preliminary Report

Extracranial Stereotactic Radioablation *: Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer

Timmerman, Robert MD [a] ... Williams, Mark MD [b]



Early SBRT Data for Inoperable IA/B NSCLC

Author	Dosing	Local control	3-year OS
Onishi *et al.*	Multiple	84% (3 yr)	57%
Nyman *et al.*	15 Gy x3	80% (3.5 yr)	55%
Uematsu *et al.*	50-60 Gy in 5-10	94% (5 yr)	66%
Timmerman *et al.*	T1: 20 Gy x3 T2: 22 Gy x3	88% (3 yr)	43%

EARLY STAGE NSCLC

RADIATION THERAPY ONCOLOGY GROUP

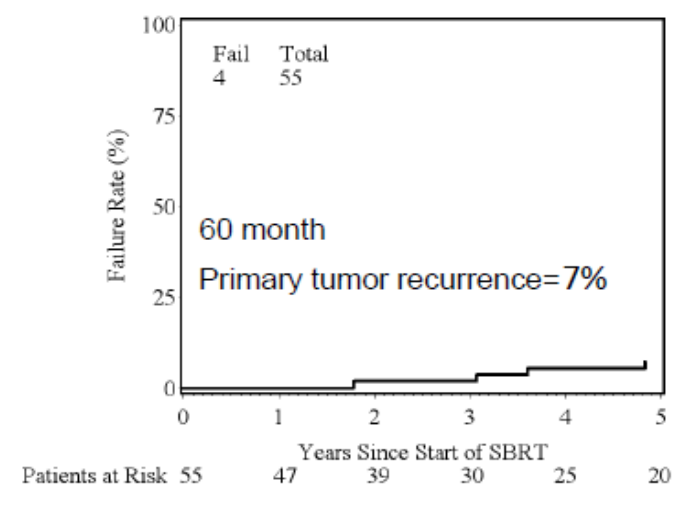
RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

- **Patients with T1, T2 (≤5 cm), T3 (≤5 cm), N0, M0 medically inoperable**
- **no CENTRAL TUMORS**
- **18 Gy x 3 over 1.5-2 wks**
- **Primary endpoint: T control**
- **55 pts, 44 T1 and 11 T2**

EARLY STAGE NSCLC

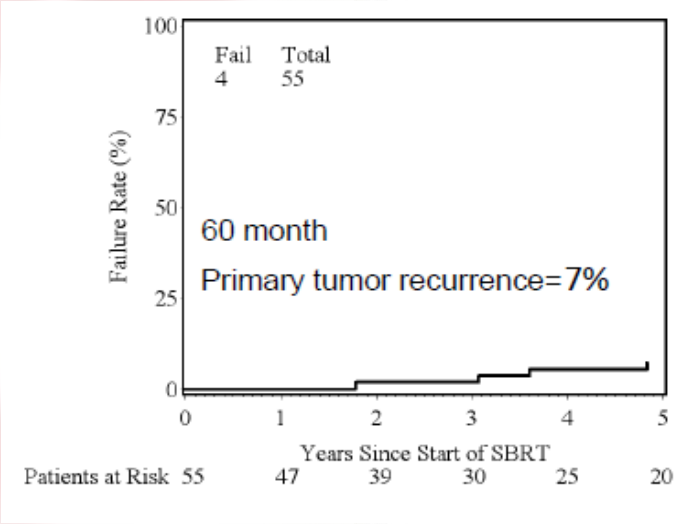
- **5-yr T recurrence (treated volume): 7%**



Timmerman et al, ASTRO 2014

EARLY STAGE NSCLC

- **5-yr T recurrence (treated volume): 7%**
- **5-yr Lobar rec: 20%**
- **5-yr T+N: 38%**
- **5-yr DM-rate: 31%**
- **5-yr OS: 40%**



Timmerman et al, ASTRO 2014

PREDOMINANT SITE OF FAILURE IS OUTSIDE THE TREATED VOLUME

EARLY STAGE NSCLC

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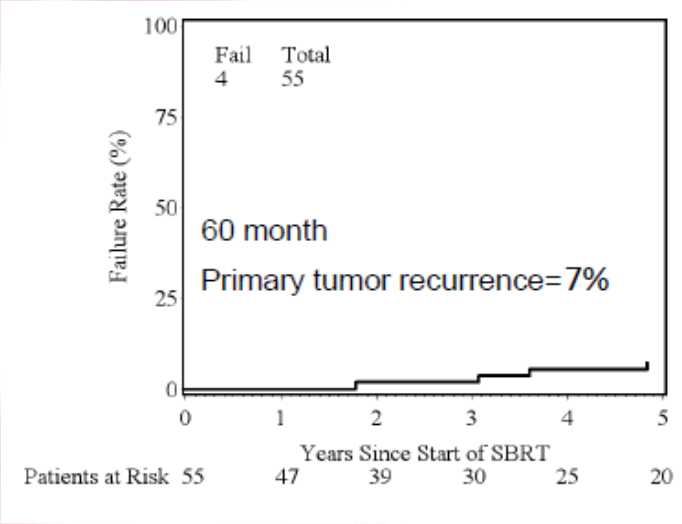

Timmerman et al, ASTRO 2014

PREDOMINANT SITE OF FAILURE IS OUTSIDE THE TREATED VOLUME

676 pts treated with SBRT, 5-YR DM rate ≈20%, median time ≈10 mths
Senthi et al, Lancet Oncol 2012

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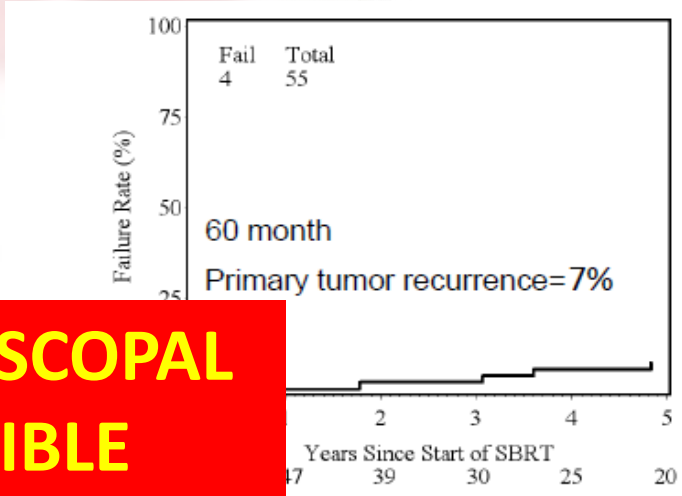


nmerman et al, ASTRO 2014

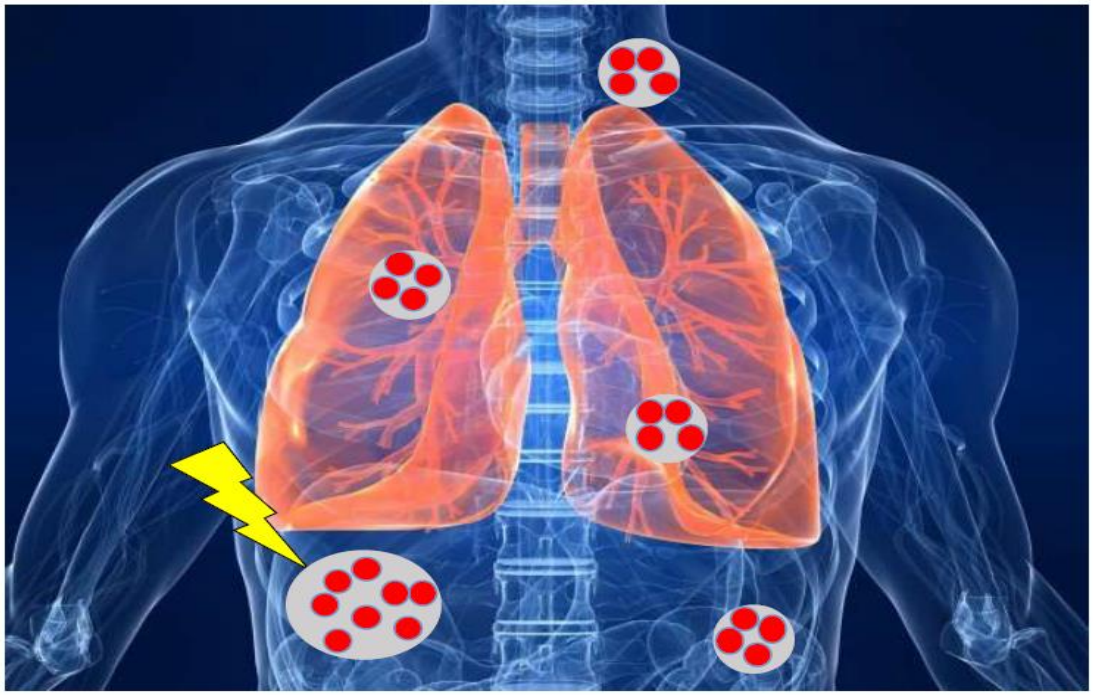
?IS PURSUING ABSCOPAL EFFECT A FEASIBLE STRATEGY IN SELECTED EARLY STAGE NSCLC

PREDOMINANT SITE OF FAILURE IS OUTSIDE THE TREATED VOLUME

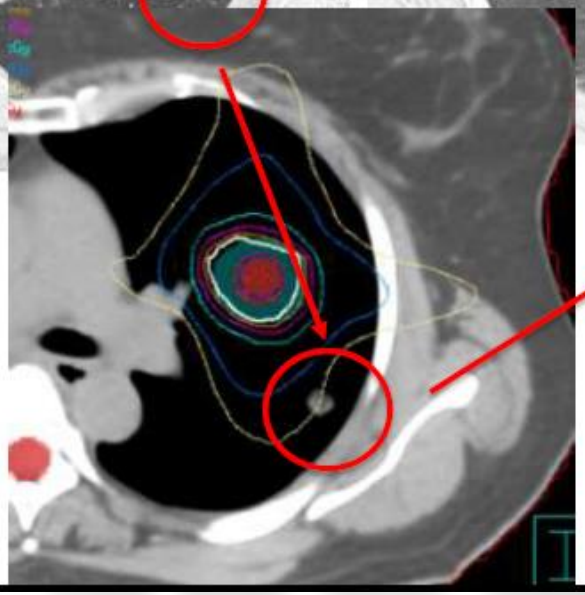
676 pts treated with SBRT, 5-YR DM rate ≈20%, median time ≈10 mths
Senthi et al, Lancet Oncol 2012

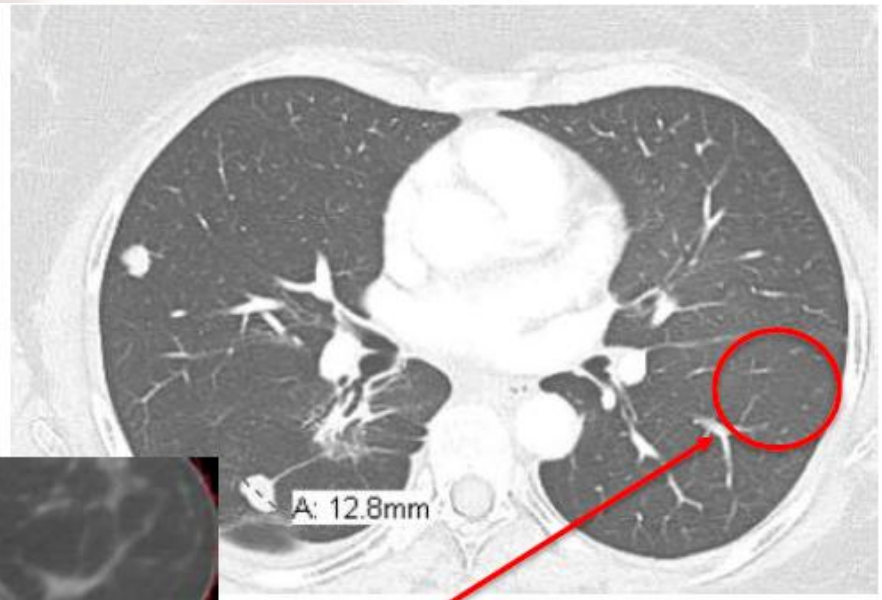
From local to abscopal

Local control or curing the patient?



1-23-17





5-10-17

Tumor got low dose scatter

Welsh, ASTRO 2017

Curr Probl Cancer 40 (2016) 25–37

Contents lists available at ScienceDirect

Curr Probl Cancer

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

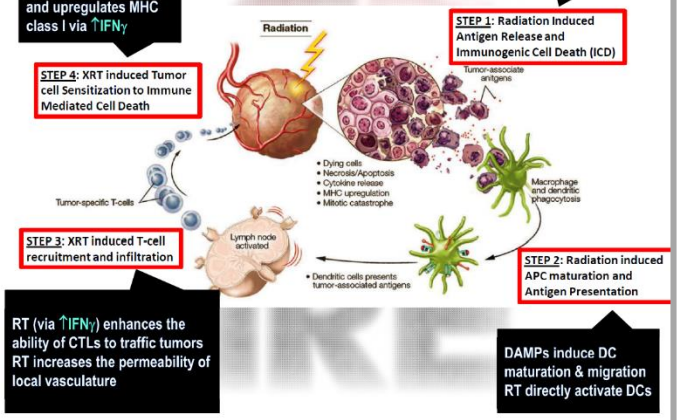
Systematic review of case reports on the abscopal effect

Yazan Abuodeh, MD, Puja Venkat, MD,
Sungjune Kim, MD, PhD

- 2 cases of NSCLC (adenoca) out of 46 cases from 1969 to 2014

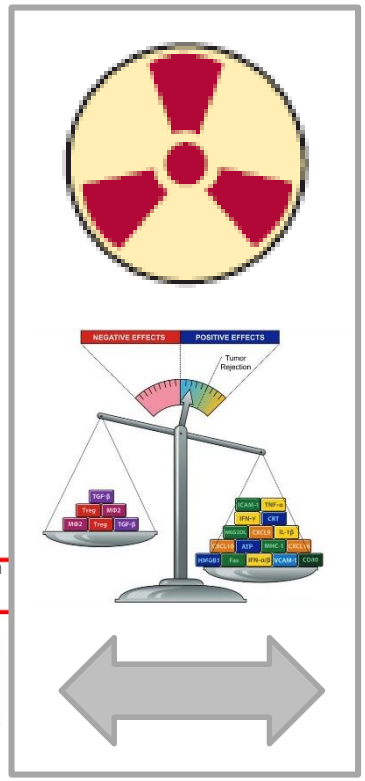
RT induces FAS/FAS-L and upregulates MHC class I via ↑IFNγ

Necrosis induces ICD; HMGB1, calreticulin & ATP promote Ag presentation by dying cells to DCs



RT (via ↑IFNγ) enhances the ability of CTLs to traffic tumors
RT increases the permeability of local vasculature

DAMPs induce DC maturation & migration
RT directly activate DCs



- Microenvironment
- Cytokine/chemokines
- Infiltrating cells
- Irradiated volume
- Dose/fractionation

PD-L1 upregulated by RT by tumor cells through IFNγ produced by CD8+ cells
TGFβ activated by RT involved in any step of cancerogenesis.... Suppresses CD8+ and polarize TAM to M2

-TAM M2-polarized are upregulated by RT
-Myeloid-Derived Suppressor Cells
-Tregs induced by TGF-β (and then

ICD is dose-dependent in vitro with higher doses being more immunogenic
DNA exonuclease Trex1 induced by RT single doses > 12-18 Gy, degrading dsDNA and reducing the immunogenic effect of RT

Irradiated volume, inclusion of regional nodes....nodal irradiation, while reducing tumor infiltrating CD8+T cells, may increase T-cell chemoattractants and antigen specific CD8+ T cells in the tumor microenvironment.

IMMUNOSTIMULATION vs IMMUNOSUPPRESSION

Adding radiotherapy to pembrolizumab immunotherapy significantly increased (abscopal) responses and outcomes (PFS & OS) in patients with metastatic non-small-cell lung cancer.

Conclusions

- IT&RT combos is a promising strategy in early stage NSCLC