Predictors of response in patients and radiation-dose impact

Session: An Immuno-oncology Primer for Physicists.

AAPM 2020: Wed July 15th 1:00-2:00 pm EDT

Eric Ford, PhD FAAPM
Professor
University of Washington
Seattle, WA

Disclosures

- None

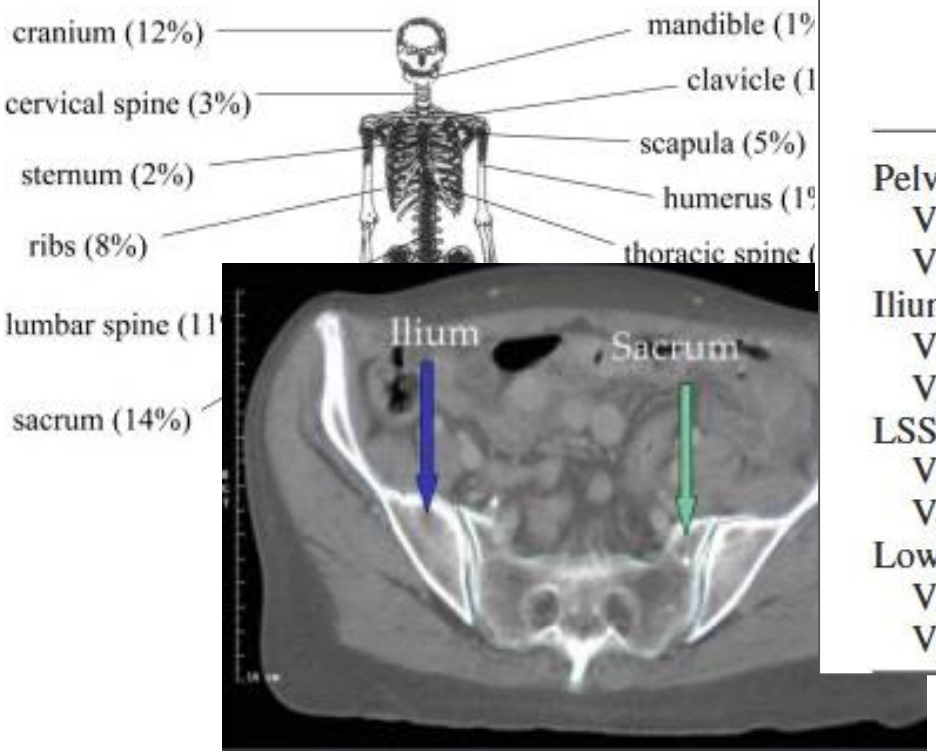
Learning Objectives

- Understand the fundamental biological underpinnings of the interaction between the immune response and radiation therapy.
- Learn about emerging data connecting immune response to radiation dose and biophysical models that describe this interaction.
- Appreciate how medical physicists might participate in IO efforts in the clinical and research space.

Outline

- RT has a systemic effect on the immune system
- Translates into outcomes
- Major challenge for combined therapies with ICI

Bone Marrow RT and Hematological Toxicity



	RTOG grade 2+ leukopenia		
	Odds ratio*	95% CI	*p*
Pelvic BM			
V_{10}	2.09	1.24–3.53	0.006†
V_{20}	1.40	1.06–1.85	0.017†
Ilium			
V_{10}	1.04	0.88–1.22	0.66
V_{20}	1.06	0.96–1.16	0.27
LSS			
V_{10}	1.66	0.96–2.88	0.070
V_{20}	1.25	1.01–1.57	0.048†
Lower pelvis			
V_{10}	1.35	1.06–1.70	0.013†
V_{20}	1.25	1.04–1.52	0.021†

L. Mell et al. Int J Radiat Oncol Biol Phys, 66(5): 1356-1365 (2006)

Effects of RT on the immune system.

Is it all about bone-marrow?

Hematological toxicity & RT: Brain

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 3, pp. 535–543, 1999
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0360-3016/99/$–see front matter

PII S0360-3016(99)00060-7

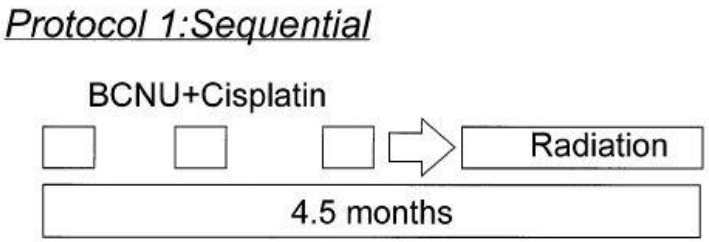
CLINICAL INVESTIGATION **Central Nervous System**

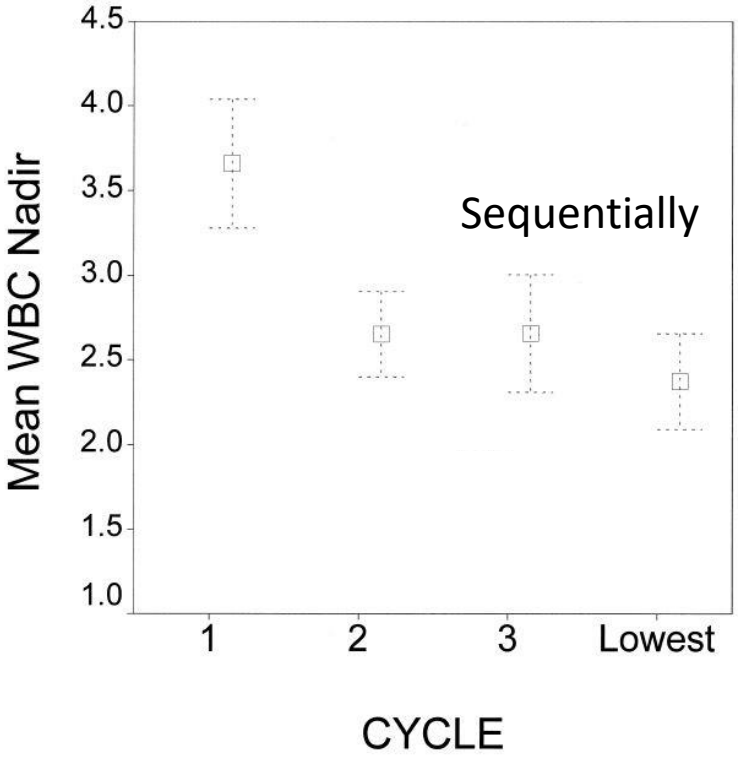
THE EFFECTS OF SEQUENTIAL VERSUS CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY ON SURVIVAL AND TOXICITY IN PATIENTS WITH NEWLY DIAGNOSED HIGH-GRADE ASTROCYTOMA

LAWRENCE KLEINBERG*, STUART A.GROSSMAN,† STEVEN PIANTADOSI,‡ MICHEL ZELTZMAN,† AND MOODY WHARAM*

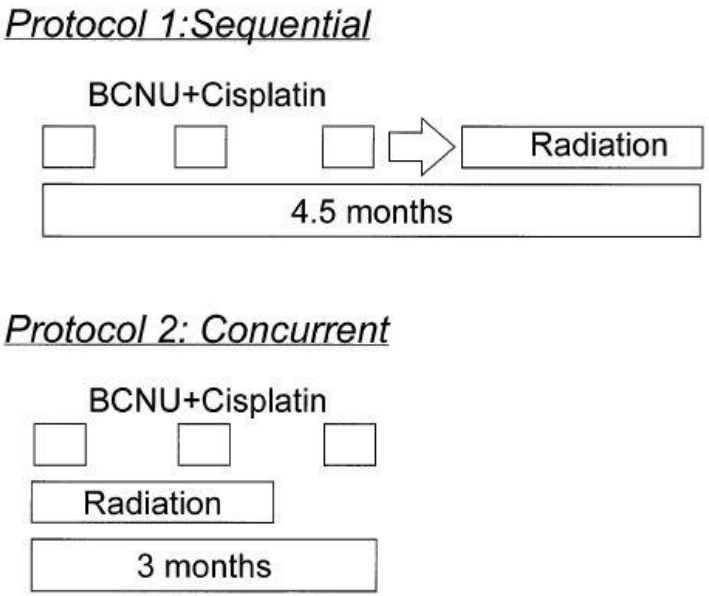
Divisions of *Radiation Oncology, †Medical Oncology, and ‡Biostatistics, Johns Hopkins Oncology Center, Baltimore, MD

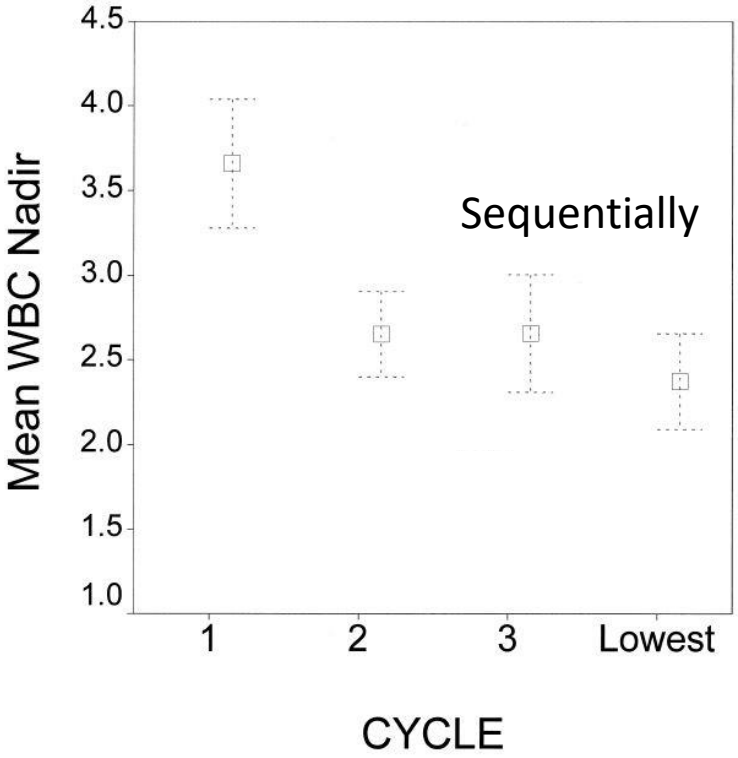
Hematological Toxicity & RT: Brain



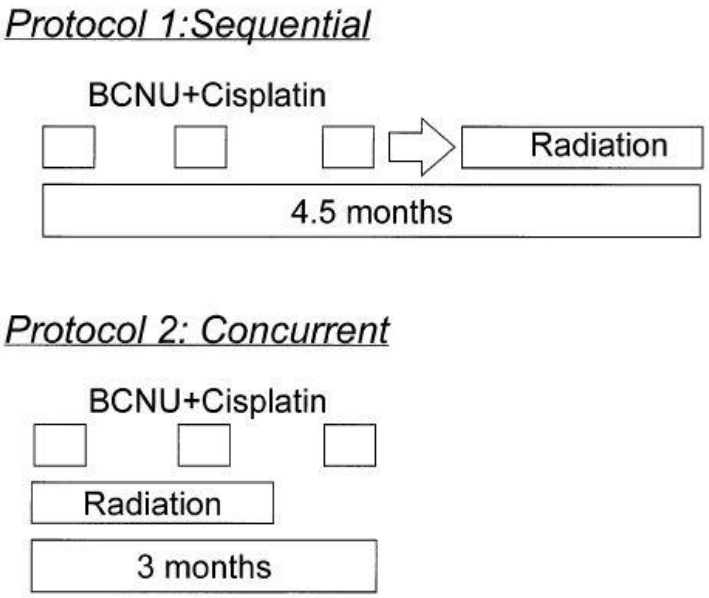


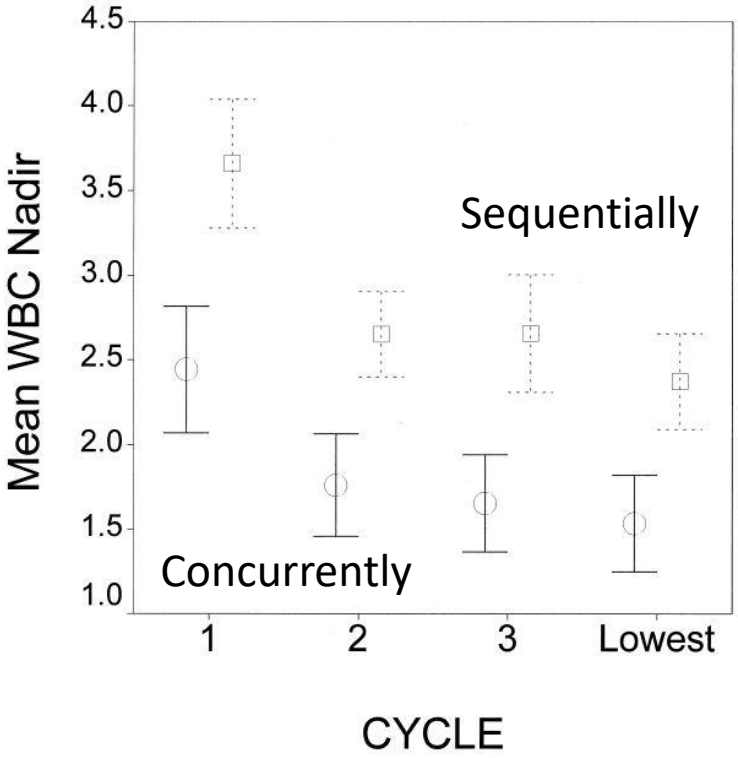
Hematological Toxicity & RT: Brain

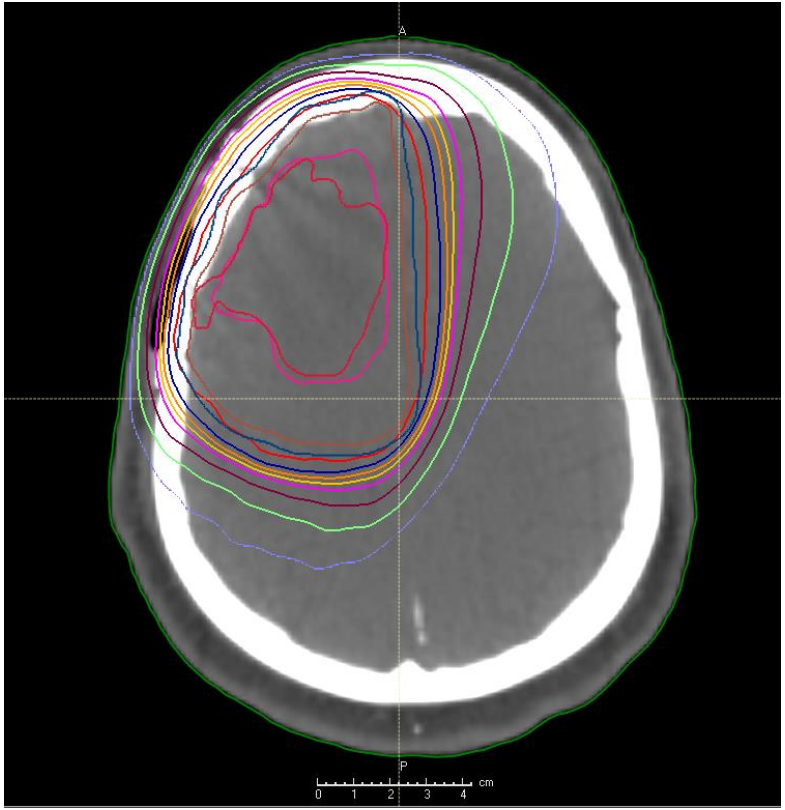




Hematological Toxicity & RT: Brain







Systemic effects
not explained by dose to
bone-marrow

GBM Study: RT + TMZ

<2015

Standard field

- 46 Gy: T1 + T2 + 1-2 cm
- 14 Gy: T1 + 1-2 cm

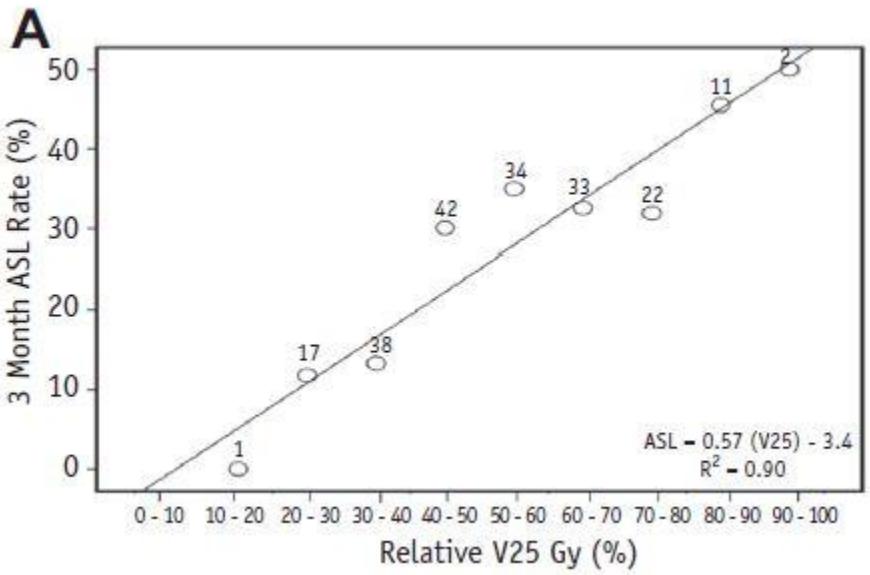
>2015

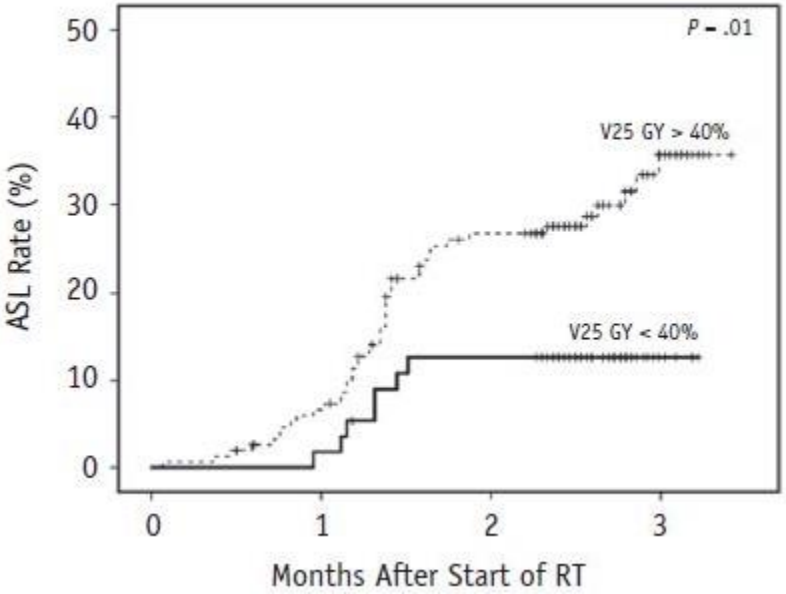
Limited-field approach

- 46 Gy: T1 + 1.5 cm
- 14 Gy: T1 + 0.5 cm

Rudra et al. Int J Radiat Oncol Biol Phys, 101(1):217-225 (2018)
Wash U

Acute Severe Lymphopenia





Rudra et al. Int J Radiat Oncol Biol Phys, 101(1):217-225 (2018)
Wash U

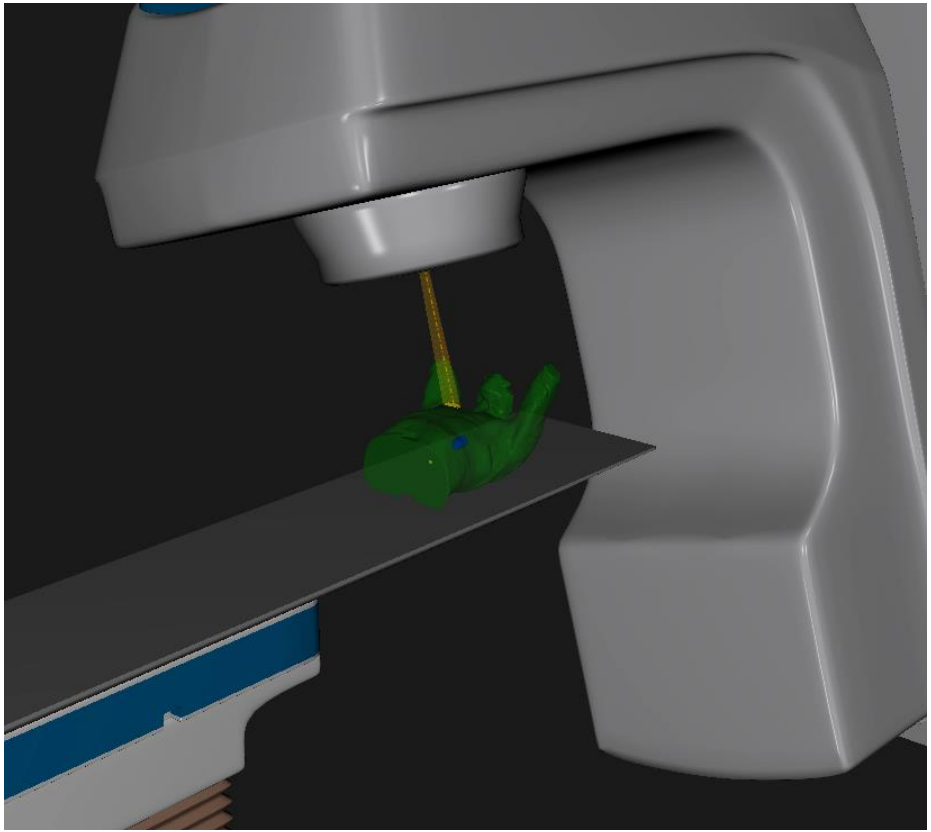
Acute Severe Lymphopenia

Table 2 Overall survival univariate and multivariate Cox regression analysis

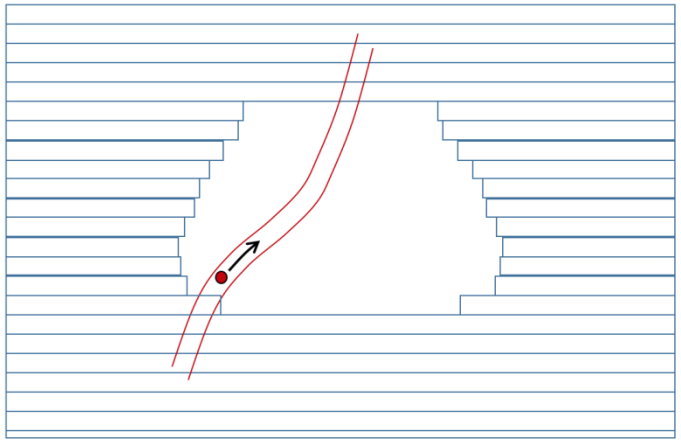
Characteristic	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI) (n = 160)	*P*
Older age	1.014 (1.001-1.027)	.034	NS	NS
Higher KPS	0.987 (0.974-1.001)	.062	NS	NS
Female sex	0.811 (0.595-1.103)	.182		
Caucasian race	0.733 (0.406-1.323)	.302		
EOR				
GTR	Ref			
STR/biopsy	1.395 (1.031-1.886)	.031	1.619 (1.126-2.327)	.009
Methylated MGMT*	0.493 (0.339-0.717)	<.001	0.469 (0.322-0.683)	<.001
Higher baseline TLC (100 cells/μL)	0.984 (0.963-1.007)	.166		
Higher baseline Dex Use (mg/d)	1.040 (1.003-1.079)	.034	NS	NS
Limited-field RT	1.246 (0.827-1.877)	.293		
RT technique (IMRT)	0.964 (0.634-1.464)	.863		
TLC < 500 cells/μL at week 6	1.454 (0.988-2.139)	.058	NS	NS
TLC < 500 cells/μL at week 12	1.488 (0.806-2.748)	.204		
ASL at any time point	1.867 (1.326-2.629)	<.001	1.831 (1.196-2.803)	.005
GTV*	1.003 (0.998-1.007)	.222		

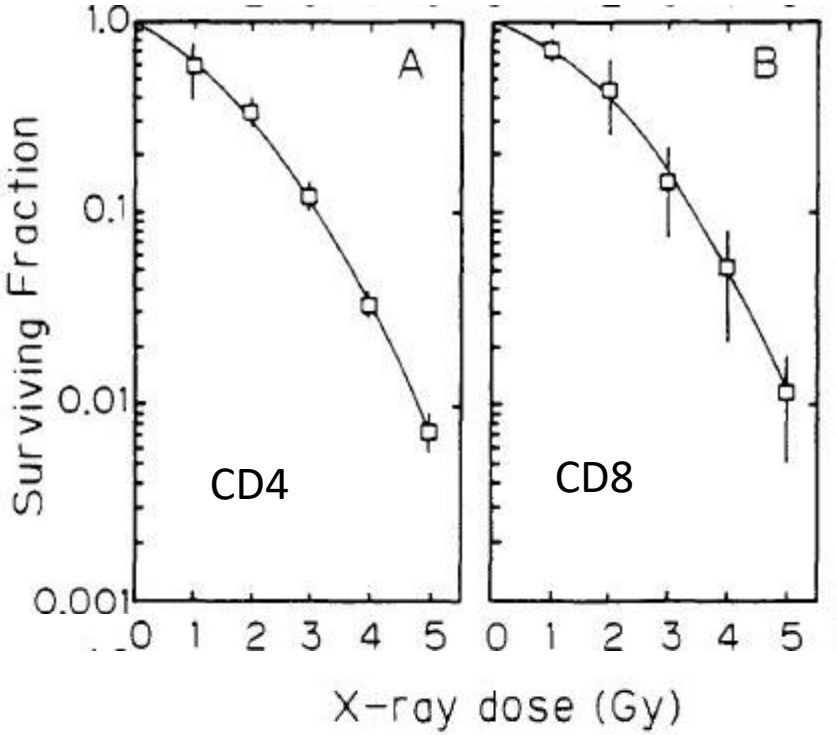
Rudra et al. Int J Radiat Oncol Biol Phys, 101(1):217-225 (2018)
Wash U

What accounts for this effect?



Lymphocytes: RT exposure & sensitivity





$D_{50} \approx 2$ Gy

Nakamura et al. Rad Res, 123:224-227 (1990)

Lymphocytes: RT exposure & sensitivity

Cancer Investigation, 31:140–144, 2013
ISSN: 0735-7907 print / 1532-4192 online
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DOI: 10.3109/07357907.2012.762780

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healthcare

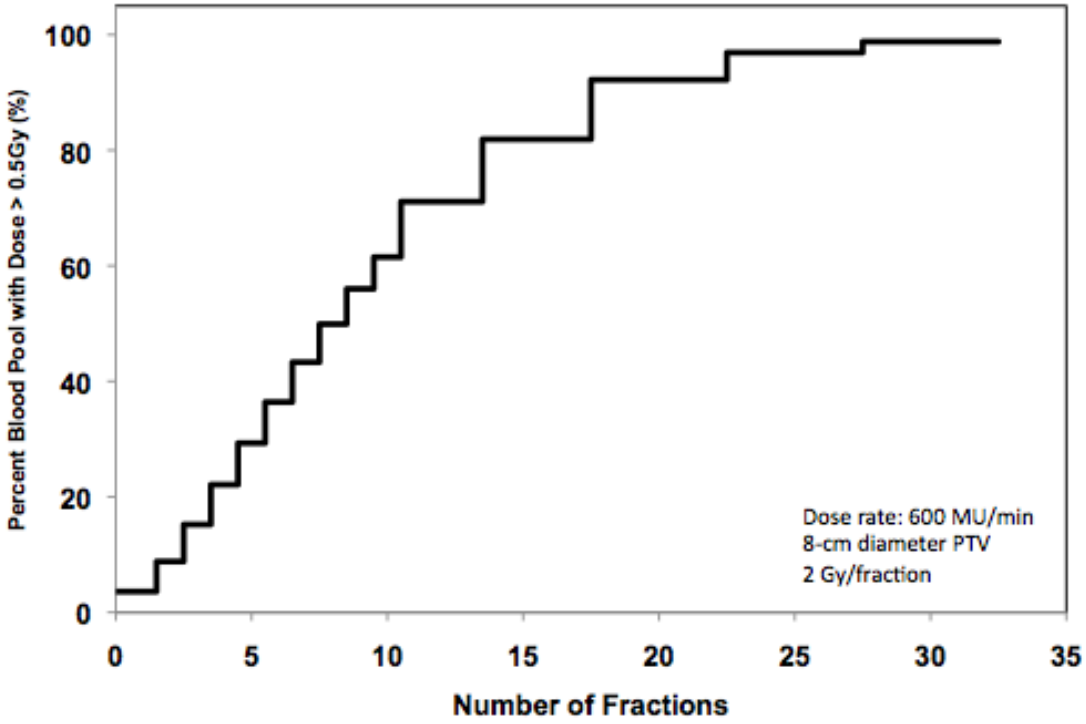
CLINICAL TRANSLATIONAL RESEARCH

The Etiology of Treatment-related Lymphopenia in Patients with Malignant Gliomas: Modeling Radiation Dose to Circulating Lymphocytes Explains Clinical Observations and Suggests Methods of Modifying the Impact of Radiation on Immune Cells

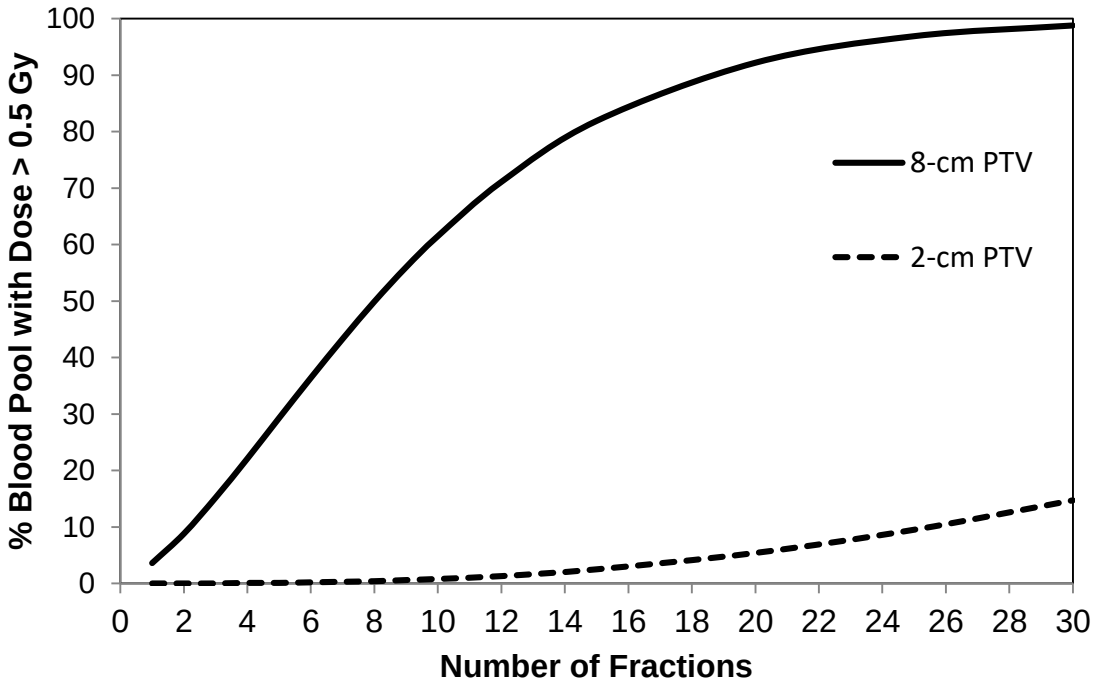
Susannah Yovino,[1] Lawrence Kleinberg,[1] Stuart A. Grossman,[2] Manisha Narayanan,[3] and Eric Ford[1]

Departments of Radiation Oncology[1] and Medical Oncology[2], and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA[3]

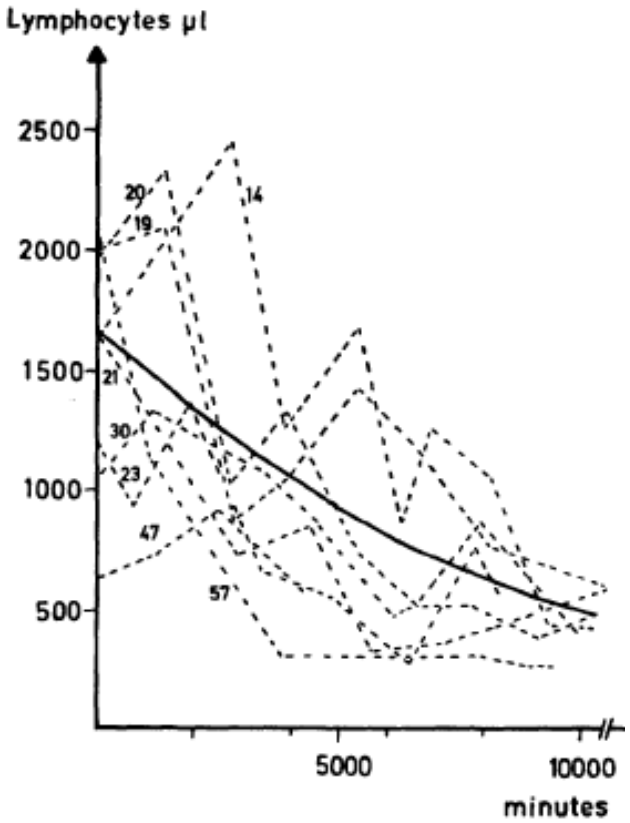
Lymphocytes: RT exposure & sensitivity



Lymphocytes: RT exposure & sensitivity



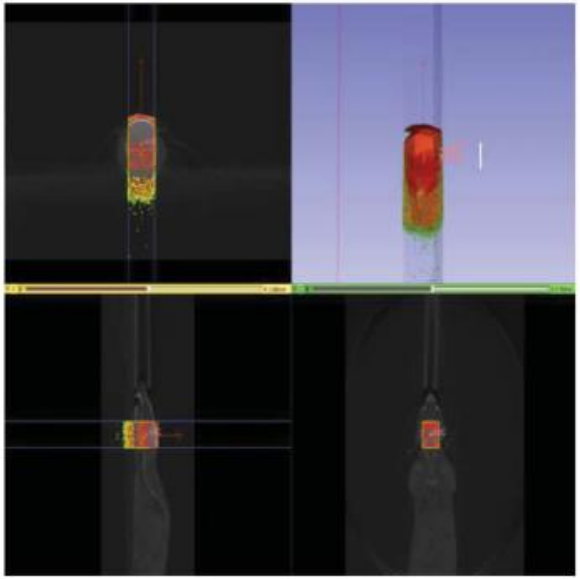
Is there any independent validation of these effect?

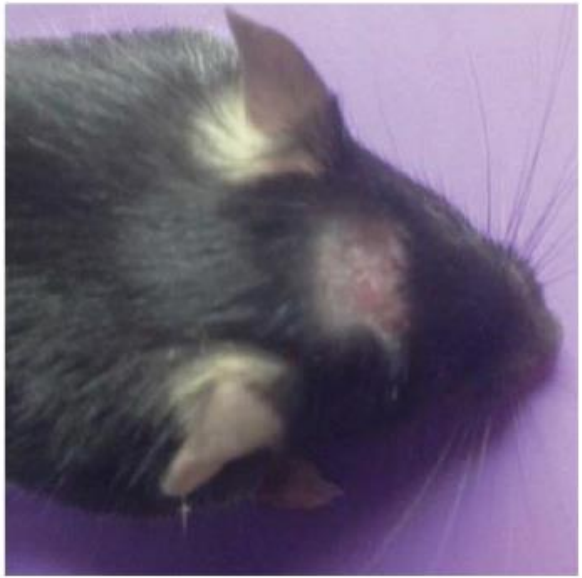


Extracorporeal irradiation of blood
Patients receiving transfusions

Weeke E.. Radiat Res 1973;56:554–9. https://doi.org/10.2307/3573724.

Murine model: Focal RT





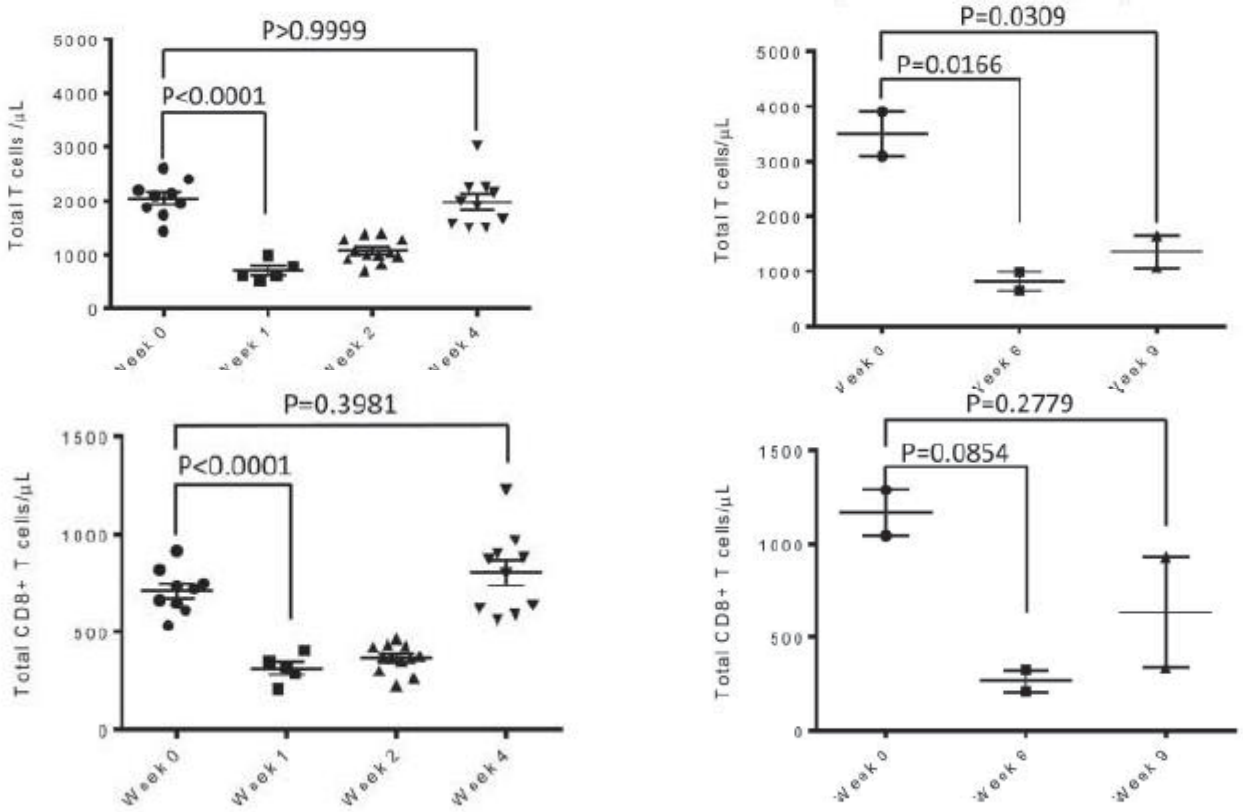
Piotrowski et al. Oncoimmunology, 7(7), e1445951 (2018)
Johns Hopkins
https://doi.org/10.1080/2162402X.2018.1445951

4Gy x 10 Fractions

2Gy x 30 Fractions

T cells
(CD45+CD3+)

CD8+ T cell
(CD45+CD3+CD4-)



Piotrowski et al. Oncoimmunology, 7(7), e1445951 (2018)

Radiation Suppresses Lymphocytes

Other clinical data

Radiotherapy and Oncology 128 (2018) 498–504

Contents lists available at ScienceDirect

Radiotherapy and Oncology

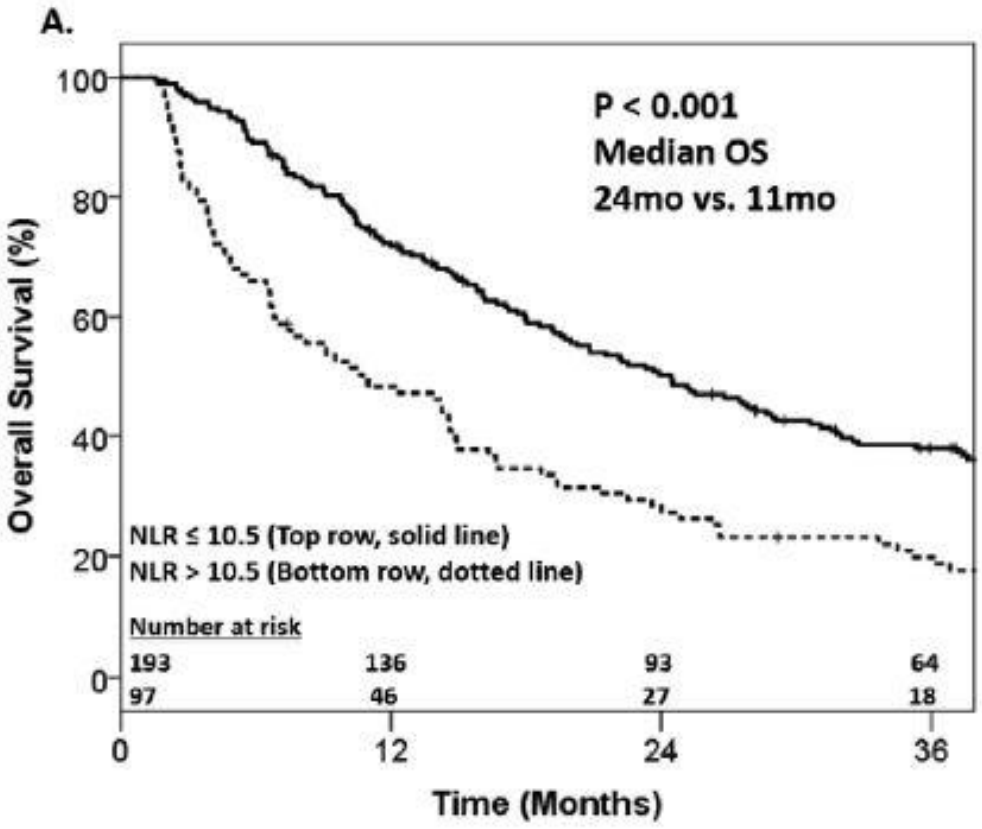
journal homepage: www.thegreenjournal.com

Lung cancer

Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer

Jessika A. Contreras [a,1], Alexander J. Lin [a,1], Ashley Weiner [b], Christina Speirs [c], Pamela Samson [a], Daniel Mullen [a], Jian Campian [d], Jeffrey Bradley [a], Michael Roach [a], Clifford Robinson [a,*]

[a] Radiation Oncology, Washington University Medical Center, St. Louis; [b] Radiation Oncology, The University of North Carolina; [c] Cancer Center of Hawaii; and [d] Medical Oncology, Washington University Medical Center, St. Louis, USA



91% of pts >Gr 3 lymphopenia at nadir

Neutrophil to Lymphocyte ratio

Treatment factors
Multivariate analysis (NLR at 4 mo):
Heart V50

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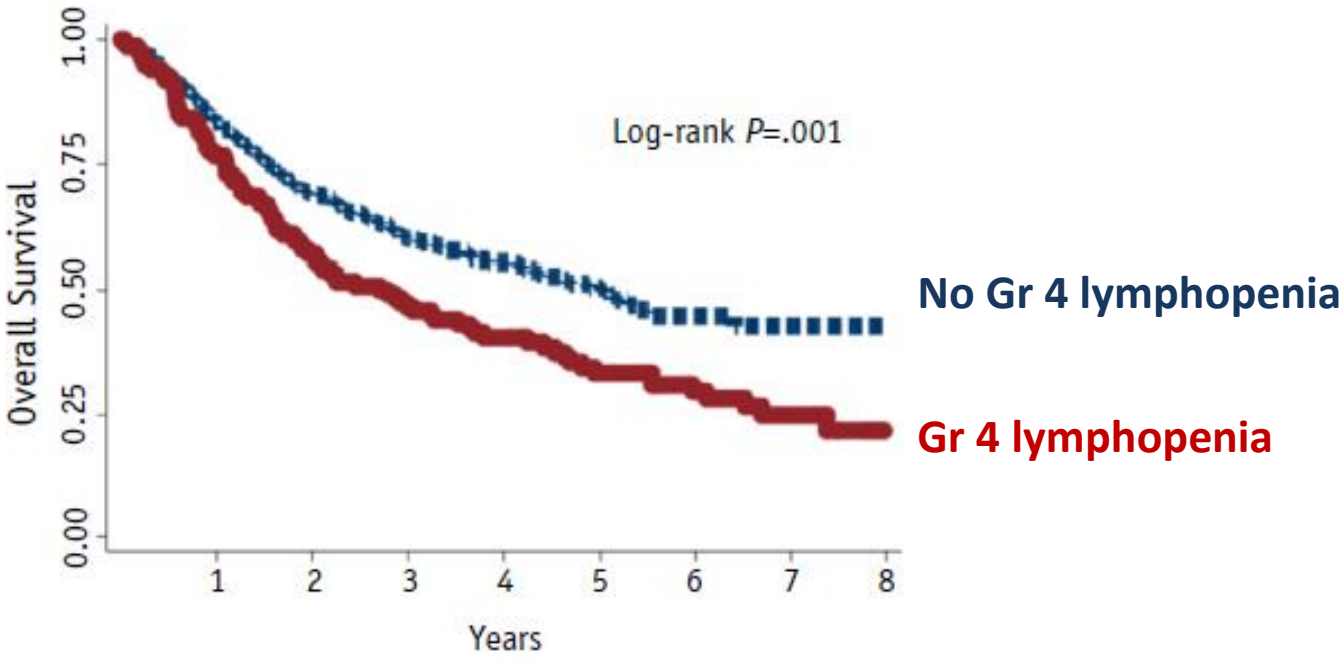
Clinical Investigation

Lymphocyte Nadir and Esophageal Cancer Survival Outcomes After Chemoradiation Therapy

Rajayogesh Davuluri, MD,[*,1] Wen Jiang, MD, PhD,[†,1] Penny Fang, MD,[†] Cai Xu, MD,[†] Ritsuko Komaki, MD,[†] Daniel R. Gomez, MD,[†] James Welsh, MD,[†] James D. Cox, MD,[†] Christopher H. Crane, MD,[‡] Charles C. Hsu, MD, PhD,[*] and Steven H. Lin, MD, PhD[†]

[*]Department of Radiation Oncology, The University of Arizona, Tucson, Arizona; [†]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and [‡]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Int J Radiation Oncol Biol Phys, Vol. 99, No. 1, pp. 128–135, 2017



Davuluri et al. IJROBP, 99(1): 128-135 (2017)

Characteristic	MVA without mean body dose			MVA with mean body dose		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age at diagnosis, y	1.02	1.00-1.04	.06	1.02	1.00-1.04	.09
CAD	0.81	0.45-1.44	.48	0.85	0.46-1.57	.61
DM	1.01	0.59-1.75	.95	1.15	0.65-2.04	.64
Tumor length	1.04	0.95-1.13	.42	0.99	0.90-1.10	.92
Tumor location, lower vs mid	2.60	1.08-6.24	.03	2.42	0.95-6.19	.06
Poor vs moderate diff	0.89	0.58-1.37	.61	0.88	0.57-1.39	.60
Adeno vs SCC	1.16	0.58-2.30	.68	0.94	0.46-1.93	.87
Tumor stage III vs I-II	1.27	0.79-2.05	.32	1.34	0.81-2.20	.25
Having surgery	0.55	0.35-0.88	.013	0.62	0.38-1.02	.063
Protons vs IMRT	0.29	0.17-0.48	<.001	0.72	0.33-1.57	.41
Mean body dose*	N/A	N/A	N/A	1.22	1.08-1.37	.001
Induction chemotherapy	1.08	0.65-1.82	.76	0.99	0.58-1.69	.97
Chemo regimen 2 vs 1	0.69	0.34-1.40	.31	0.81	0.39-1.69	.58
Chemo regimen 3 vs 1	0.49	0.29-0.85	.01	0.50	0.28-0.88	.02
Chemo regimen 4 vs 1	1.41	0.64-3.13	.39	1.42	0.62-3.25	.41

Davuluri et al. IJROBP, 99(1): 128-135 (2017)

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Clinical Investigation

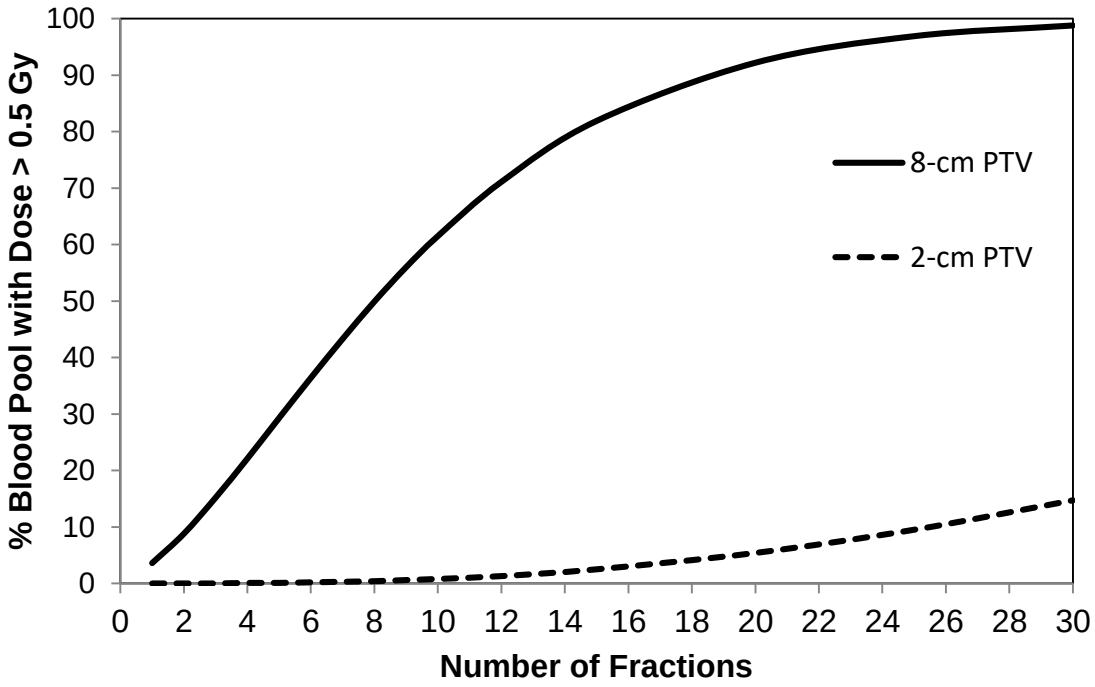
Lymphocyte Nadir and Esophageal Cancer Survival Outcomes After Chemoradiation Therapy

Rajayogesh Davuluri, MD,[*,1] Wen Jiang, MD, PhD,[†,1] Penny Fang, MD,[†] Cai Xu, MD,[†] Ritsuko Komaki, MD,[†] Daniel R. Gomez, MD,[†] James Welsh, MD,[†] James D. Cox, MD,[†] Christopher H. Crane, MD,[‡] Charles C. Hsu, MD, PhD,[*] and Steven H. Lin, MD, PhD[†]

[*]Department of Radiation Oncology, The University of Arizona, Tucson, Arizona; [†]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and [‡]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Int J Radiation Oncol Biol Phys, Vol. 99, No. 1, pp. 128–135, 2017

Lymphocytes: RT exposure & sensitivity



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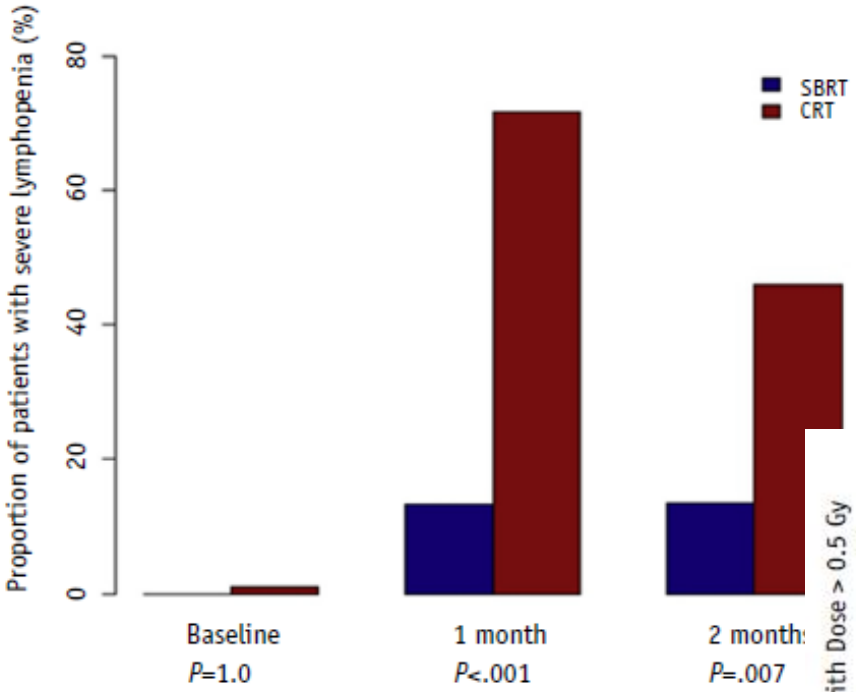
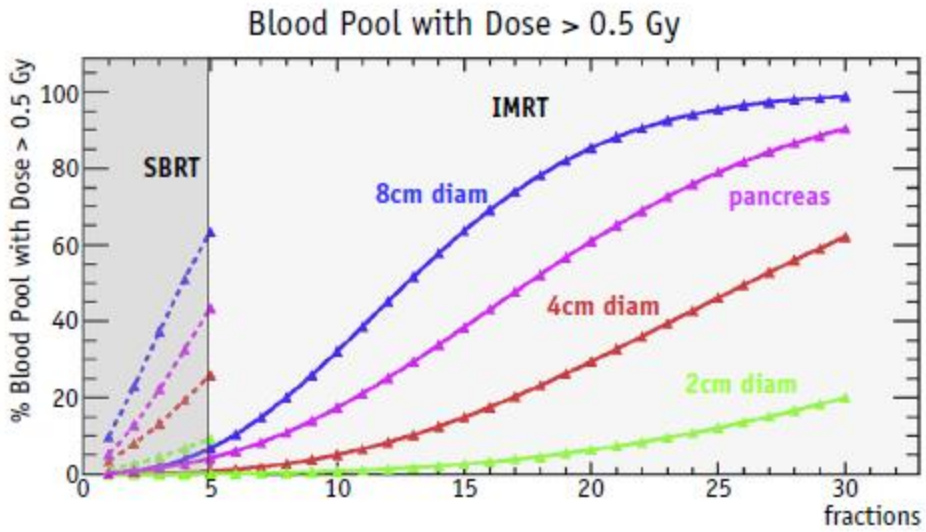
Clinical Investigation

Lymphocyte-Sparing Effect of Stereotactic Body Radiation Therapy in Patients With Unresectable Pancreatic Cancer

Aaron T. Wild, MD,* Joseph M. Herman, MD, MSc,† Avani S. Dholakia, MD,† Shalini Moningi, BA,† Yao Lu, ScM,‡ Lauren M. Rosati, BS,† Amy Hacker-Prietz, PA-C,† Ryan K. Assadi, BS,† Ali M. Saeed, PhD,† Timothy M. Pawlik, MD, MPH, PhD,§ Elizabeth M. Jaffee, MD,‖ Daniel A. Laheru, MD,‖ Phuoc T. Tran, MD, PhD,† Matthew J. Weiss, MD,§ Christopher L. Wolfgang, MD, PhD,§ Eric Ford, PhD,¶ Stuart A. Grossman, MD,‖ Xiaobu Ye, MD,‡ and Susannah G. Ellsworth, MD†

Int J Radiation Oncol Biol Phys, Vol. 94, No. 3, pp. 571–579, 2016


Proportion of patients with severe lymphopenia (%)
0
20
40
60
80
SBRT
CRT
Baseline
P=1.0
1 month
P<.001
2 months
P=.007


Blood Pool with Dose > 0.5 Gy
% Blood Pool with Dose > 0.5 Gy
0
20
40
60
80
100
SBRT
IMRT
8cm diam
pancreas
4cm diam
2cm diam
0
5
10
15
20
25
30
fractions

Conclusions

- Radiation affects the immune system … more than bone-marrow irradiation
- Field (tumor) size has an enormous effect
- Modality, technique, dose/fractionation all seem to have some impact
- Impacts overall survival

What is the impact of these effects when **combining RT with immune-modulating agents** (e.g. inhibitors to CTLA-4 or PDL-1)?

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Clinical Investigation

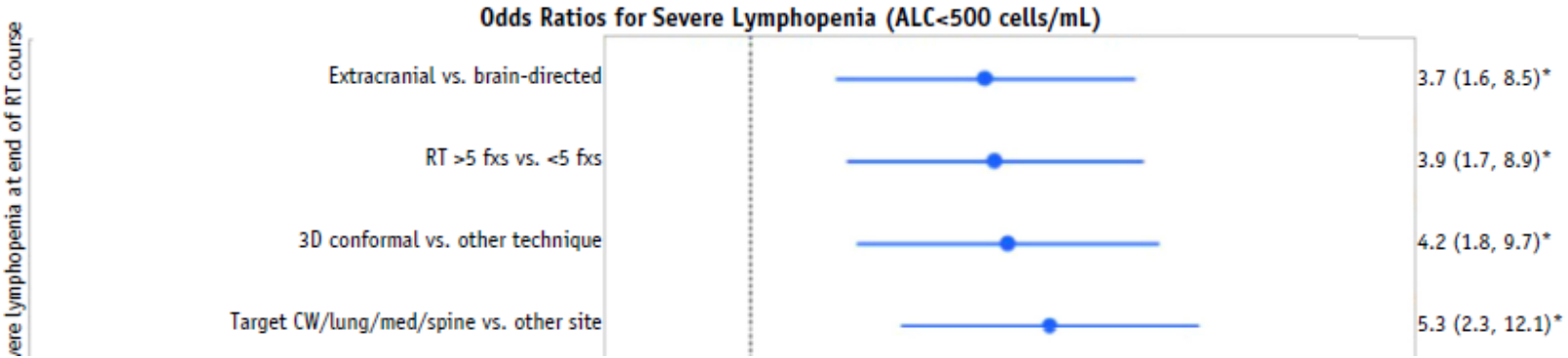
The Impact of Radiation Therapy on Lymphocyte Count and Survival in Metastatic Cancer Patients Receiving PD-1 Immune Checkpoint Inhibitors

Luke R.G. Pike, MD, DPhil,[*,†] Andrew Bang, MD,[*,‡] Brandon A. Mahal, MD,[*,†] Allison Taylor, RNP,[*] Monica Krishnan, MD,[*] Alexander Spektor, MD, PhD,[*] Daniel N. Cagney, MD,[*] Ayal A. Aizer, MD,[*] Brian M. Alexander, MD,[*] Osama Rahma, MD,[*] Tracy Balboni, MD,[*] Patrick A. Ott, MD, PhD,[*] F. Stephen Hodi, MD,[*] and Jonathan D. Schoenfeld, MD MPH[*]

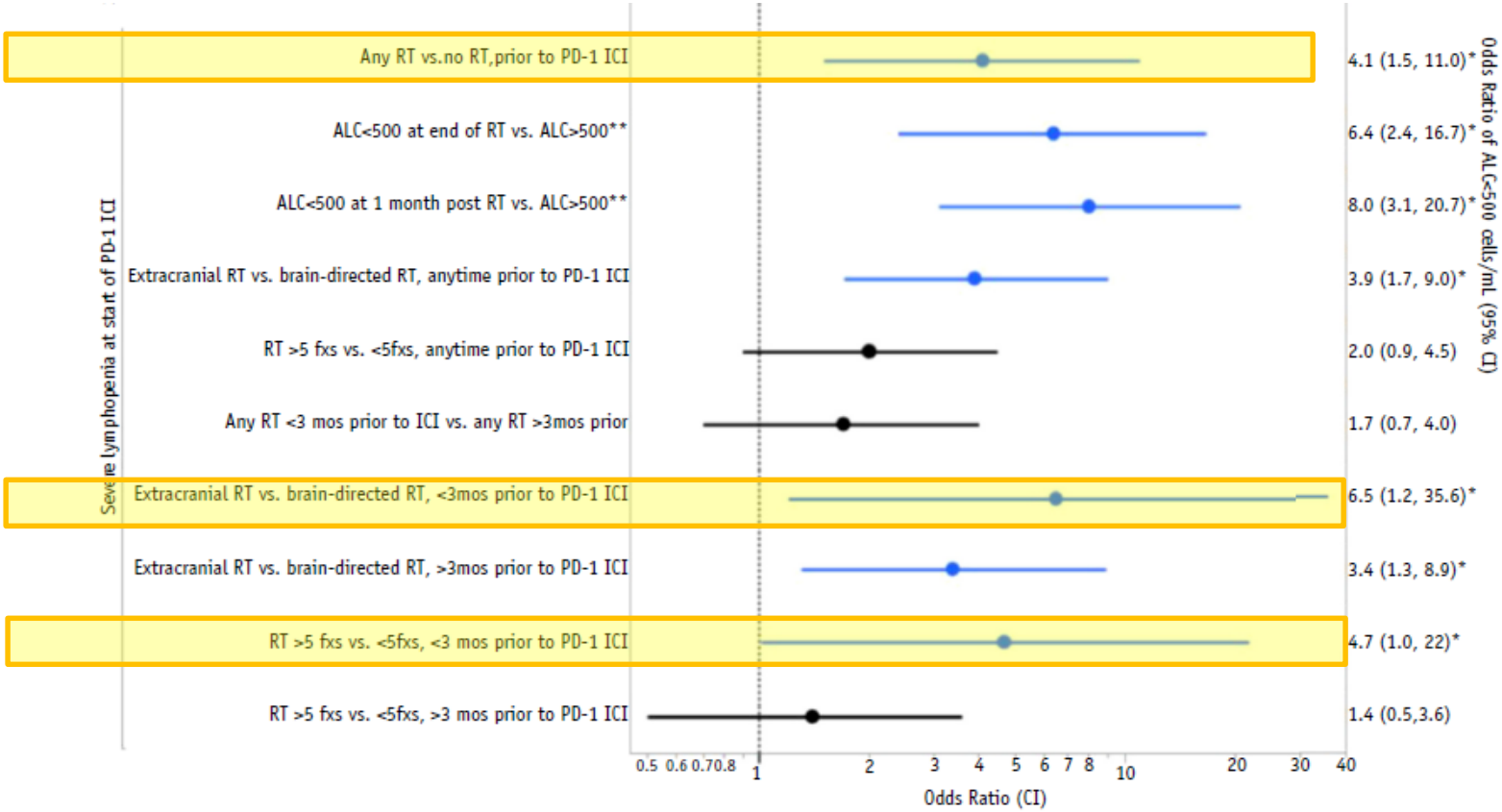
*Brigham and Women's Hospital and Dana-Farber/Harvard Cancer Center, Boston, Massachusetts; †Harvard Radiation Oncology Program, Massachusetts General Hospital, Boston, Massachusetts; and ‡Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

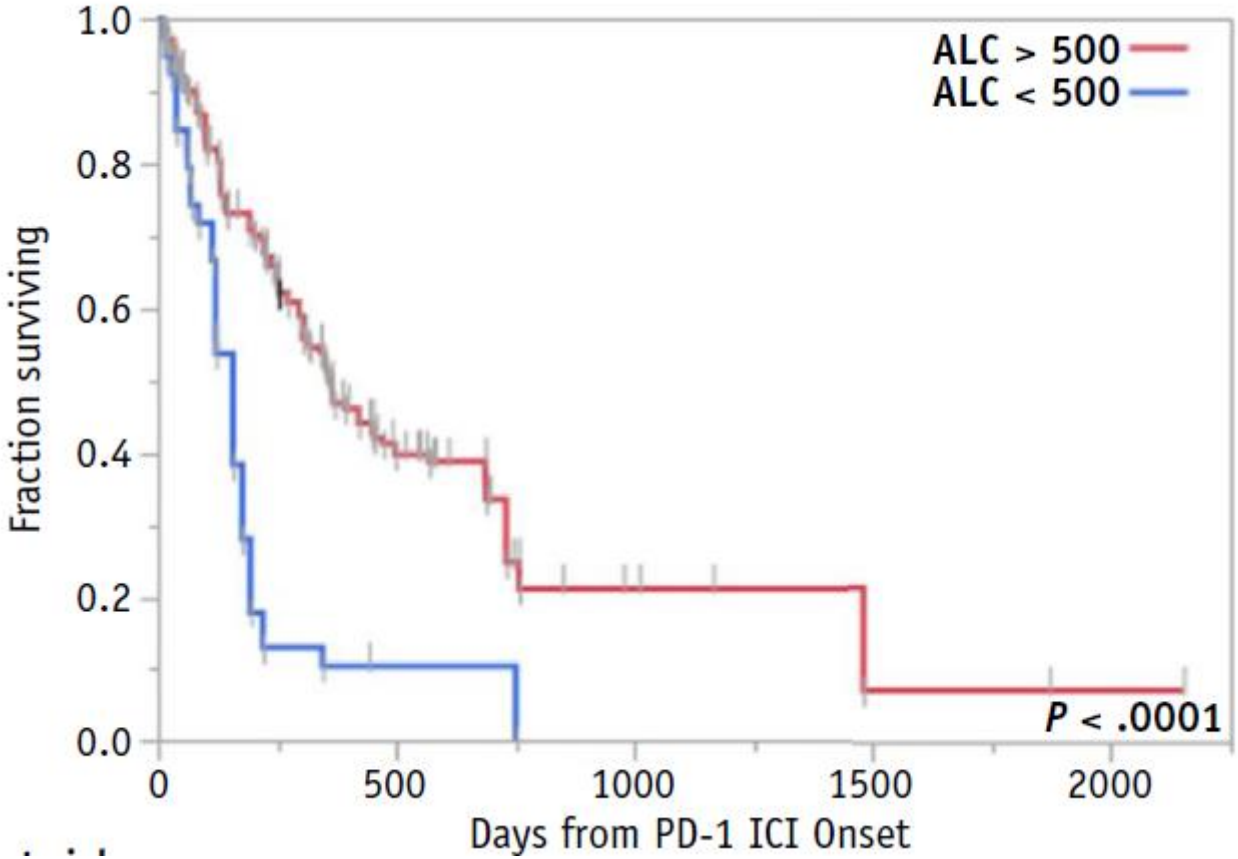
Int J Radiation Oncol Biol Phys, Vol. 103, No. 1, pp. 142–151, 2019

Pts receiving RT before ICI



Pts receiving RT before ICI




ALC > 500
ALC < 500
Fraction surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000
Days from PD-1 ICI Onset
P < .0001

The Future (physics)

- Small fields
- Hypofractionation
- Control dose distribution
- Fast delivery
- **Need good models!**

***Thank you*!**

eford@uw.edu