

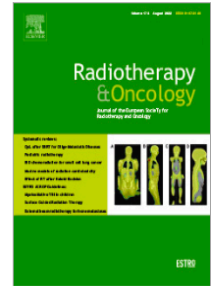


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Original Article

Impact of radiation dose to the immune cells in unresectable or stage III non-small cell lung cancer in the durvalumab era



Neal S. McCall ^{a,*}, Hamilton S. McGinnis ^a, James R. Janopaul-Naylor ^a, Aparna H. Kesarwala ^a, Sibotian ^a, William A. Stokes ^a, Joseph W. Shelton ^a, Conor E. Steuer ^b, Jennifer W. Carlisle ^b, Ticianaleal ^b, Suresh S. Ramalingam ^b, Jeffrey D. Bradley ^a, Kristin A. Higgins ^a

^a Winship Cancer Institute of Emory University, Department of Radiation Oncology; and ^b Winship Cancer Institute of Emory University, Department of Hematology & Medical Oncology, United States

Dr. Nikhil Kalyani
Radiation Oncologist



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Introduction

LA Lung cancer: Common

PACIFIC Trial: CRT followed by Durvalumab

RTOG 0617:

Poor Outcomes with Escalated dose 74 Gy

Hypothesis: High doses to circulating immune cells

Depletion of antitumour immune cells

EDIC: More than 6 Gy, 8% / Gy decline in OS

Similar data with Durvalumab NA



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Model to calculate EDIC:

Mean heart dose, mean lung dose, and integrated total dose volume (ITDV)

$$EDIC = 0.12 * MLD + 0.08 * MHD + \left[0.45 + 0.35 * 0.85 * \left(\frac{\#fractions}{45} \right)^{\frac{1}{2}} \right] * ITDV / (61.8 * 10^3)$$

Jim et al

Material and Methods

2017-202, **Retrospective study**, n=100

Stage II / III Lung ca

CCRT f/b at least 1 cycle Durvalumab

Less than 25# excluded

4D CT done for all, 3DCRT or IMRT



Material and Methods

Primary EP: OS; Secondary EP: PFS and LRC

Exploratory EP: Time to Brain Mets

EDIC calculated from TPS parameters

Divided in to more than 6 Gy (n=54) and less than 6 Gy (n=46)

Analyzed as both Categorical and Cont variable



Patient and treatment characteristics.

	EDIC ≤ 6 Gy (N = 46)	EDIC > 6 Gy (N = 54)	P-Value	
Mean Age (years)	65.65 ± 8.26	65.24 ± 7.78	0.798 [†]	
Male	26 (56.5 %)	37 (68.5 %)	0.216	
Race	Black	25 (54.3 %)	26 (48.1 %)	0.336*
	White	18 (39.1 %)	27 (50.0 %)	
	Asian	3 (6.5 %)	1 (1.9 %)	
ECOG PS	0	19 (41.3 %)	22 (40.7 %)	0.825
	1	26 (56.5 %)	29 (53.7 %)	
	2	1 (2.2 %)	3 (5.6 %)	
Smoking History	Never Smoker	4 (8.7 %)	4 (7.4 %)	0.777*
	Former Smoker	6 (13.0 %)	10 (18.5 %)	
	Current Smoker	36 (78.3 %)	40 (74.1 %)	
PET/CT Staging		44 (95.7 %)	50 (92.6 %)	0.684
AJCC Stage	II	3 (6.5 %)	0 (0.0 %)	<0.001*
	IIIA	28 (60.9 %)	13 (24.1 %)	
	IIIB	12 (26.1 %)	38 (70.4 %)	
	IIIC	3 (6.5 %)	3 (5.6 %)	
Histology	Squamous Cell Carcinoma	16 (34.8 %)	22 (40.7 %)	0.847
	Adenocarcinoma	24 (52.2 %)	26 (48.1 %)	
	Other	6 (13.0 %)	6 (11.1 %)	
PD-L1 Status	PD-L1 ≥ 1 %	15 (32.6 %)	22 (40.7 %)	0.646
	PD-L1 < 1 %	10 (21.7 %)	9 (16.7 %)	
	Unknown	21 (45.7 %)	23 (42.6 %)	
Chemotherapy Regimen	Carboplatin + Paclitaxel	42 (91.3 %)	46 (85.2 %)	0.558*
	Cisplatin + Etoposide	1 (2.2 %)	5 (9.3 %)	
	Cisplatin + Pemetrexed	1 (2.2 %)	1 (1.9 %)	
	Carboplatin + Pemetrexed	2 (4.3 %)	2 (3.7 %)	
Median Prescription RT Dose Delivered (Gy)	60 (56–66)	60 (60–70)	0.715 [†]	
RT Modality	IMRT	36 (78.3 %)	46 (85.2 %)	0.332
	IMPT	7 (15.2 %)	5 (9.3 %)	
	3D-CRT	2 (4.3 %)	0 (0.0 %)	
	3D-CRT + IMRT	0 (0.0 %)	2 (3.7 %)	
	IMRT + IMPT	1 (2.2 %)	1 (1.9 %)	
Median GTV (cc)	42.0 (3.2–400.0)	170.3 (13.2–1497.3)	<0.001 [†]	
Median Time from CCRT to Durvalumab (Days)	30 (11–125)	26 (7–99)	0.137 [†]	
Median Months of Durvalumab	12 (1–12)	3.5 (1–12)	<0.001 [†]	
Discontinuation of Durvalumab due to Toxicity	7 (15.2 %)	13 (24.1 %)	0.270	

Results

100 patients,

Med FU: 23.7 months

Dmean:

Heart: 10.5 Gy, Lung: 13.7 Gy, Total body: 9.5 Gy

At LFU: 29 pts died, 27 due to disease progression

Brain metastasis: 11 patients, 9 in EDIC more than 6 Gy



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EDIC more than 6 Gy Vs Less than 6 Gy

Med OS: 29 mths Vs NR; $p= 0.001$

Med PFS: 19.4 mths Vs NR; $p=0.001$

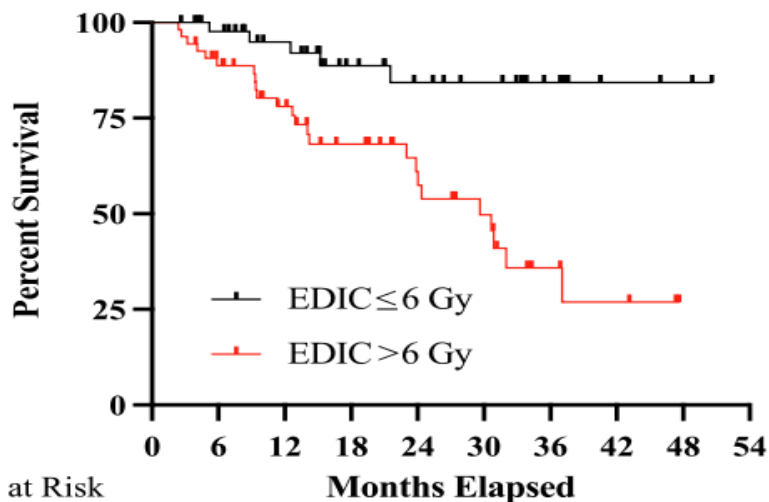
Med LRC: 34 mths Vs NR; $p= 0.022$

Med TTBM: 34 mths Vs NR; $p=0.003$



A.

Overall Survival

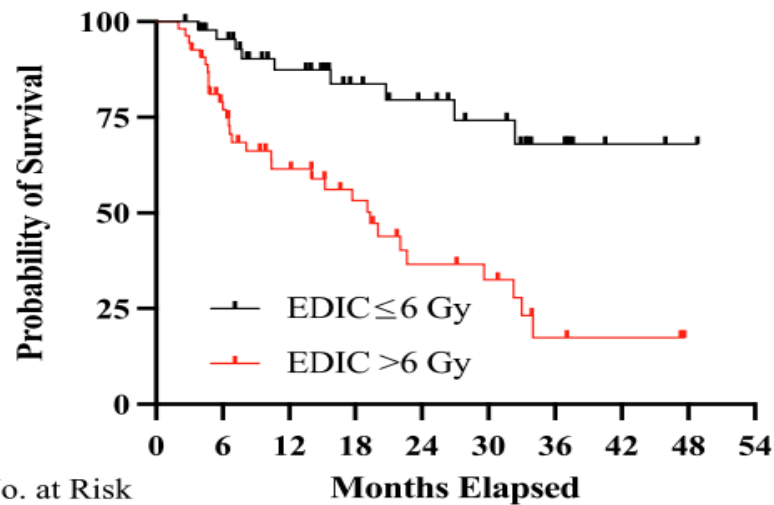


No. at Risk

	0	6	12	18	24	30	36	42	48
—	46	42	34	24	19	16	10	4	3
—	54	46	35	26	18	13	6	4	1

B.

Progression-Free Survival

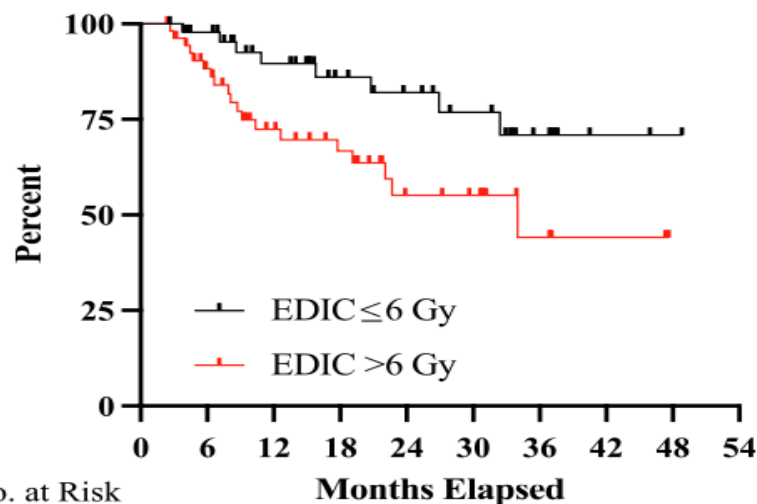


No. at Risk

	0	6	12	18	24	30	36	42	48
—	46	41	31	22	18	14	8	3	2
—	54	39	26	19	11	9	4	3	1

C.

Locoregional Control

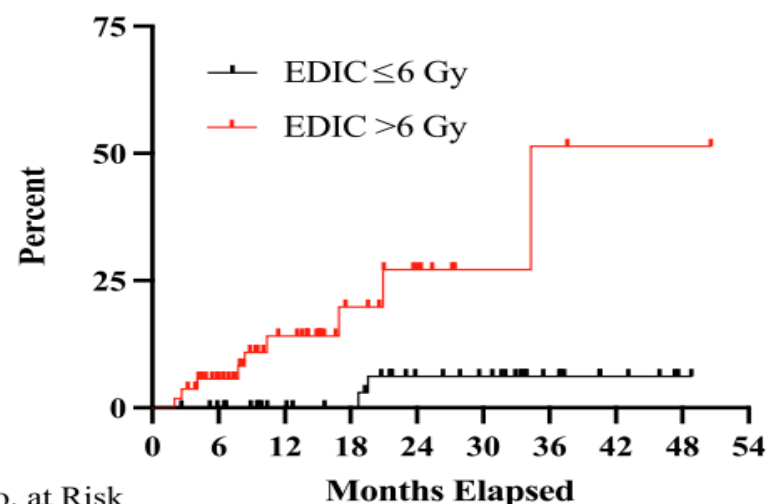


No. at Risk

	0	6	12	18	24	30	36	42	48
—	46	42	32	23	19	15	8	3	2
—	54	42	29	23	13	11	5	3	1

D.

Time To Brain Metastasis



No. at Risk

	0	6	12	18	24	30	36	42	48
—	46	44	37	34	25	22	13	6	2
—	54	44	27	14	9	4	4	3	1

Multivariate Analysis

		OS (Categorical)		OS (Continuous)	
		HR (95 %CI)	P-value	HR (95 %CI)	P-value
AJCC Stage	II-III A	-ref-	-ref-	-ref-	-ref-
	IIIB	1.93 (0.79-4.71)	0.150	-	-
	IIIC	4.86 (1.21-18.15)	0.025	-	-
Histology	Squamous Cell Carcinoma	-ref-	-ref-	-ref-	-ref-
	Adenocarcinoma	0.24 (0.10-0.56)	0.001	0.29 (0.13-0.67)	0.003
	Other	0.31 (0.07-1.41)	0.131	0.40 (0.09-1.74)	0.222
EDIC (continuous, per 1 Gy)		n/a	n/a	1.35 (1.16-1.57)	<0.001
EDIC > 6 Gy		4.15 (1.52-11.32)	0.006	n/a	n/a

		PFS (Categorical)		PFS (Continuous)	
		HR (95 %CI)	P-value	HR (95 %CI)	P-value
Age (per 1 year)		-	-	-	-
Female		0.43 (0.20-0.93)	0.033	-	-
AJCC Stage	II-III A	-ref-	-ref-	-ref-	-ref-
	IIIB	-	-	-	-
	IIIC	-	-	-	-
GTV (per 1 cc)		-	-	-	-
EDIC (continuous, per 1 Gy)		n/a	n/a	1.52 (1.30-1.79)	<0.001
EDIC > 6 Gy		3.79 (1.80-8.00)	<0.001	n/a	n/a

		LRC (categorical)		LRC (continuous)	
		HR (95 %CI)	P-value	HR (95 %CI)	P-value
Female		-	-	-	-
AJCC Stage	II-III A	-ref-	-ref-	-ref-	-ref-
	IIIB	-	-	-	-
	IIIC	-	-	-	-
Histology	Squamous Cell Carcinoma	-ref-	-ref-	-ref-	-ref-
	Adenocarcinoma	0.30 (0.13-0.70)	0.005	0.31 (0.13-0.73)	0.007
	Other	0.52 (0.19-2.32)	0.520	0.54 (0.18-2.23)	0.485
GTV (per 1 cc)		1.00 (1.00-1.01)	0.030	-	-
EDIC (continuous, per 1 Gy)		n/a	n/a	1.34 (1.13-1.60)	<0.001
EDIC > 6 Gy		2.66 (1.15-6.18)	0.023	n/a	n/a

Discussion

Incidental radiation dose to immune cells in the peripheral blood partially negate the benefit of immunotherapy

Radiation **double edged sword**:

immunostimulatory and immuno- suppressive

Higher EDIC predicting worse OS, PFS, and LRC even after accounting for other highly prognostic covariates, such as disease stage and GTV



Discussion

Brain metastases reduced with the addition of consolidative
Durvalumab

Still **most common** extra-thoracic site of disease progression

Optimizing radiation plans with EDIC-specific planning goals
reduce the dose to the immune cells and thereby potentially
improve disease control and OS



“There are things known and there are things unknown, and in between that are the doors of perception.”



Thank You...