

Composite and Total Toxicity Burden Following Induction Chemoimmunotherapy and Definitive Radiation in Stage II-III NSCLC

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INTRODUCTION

- Induction chemoimmunotherapy (chemoIO) followed by definitive radiotherapy is an emerging treatment strategy for stage II-III non-small cell lung cancer (1,2)
- The toxicity profile of this sequencing approach remains incompletely characterized.
- We report toxicity outcomes from two institutional registry cohorts using both a binary composite CTCAEv5 endpoint and a severity-weighted Total Toxicity Burden (TTB) score, with goals of quantifying the RT toxicity signal in the post-induction setting and in an upfront unresectable NSCLC population.

METHODS

Two prospective registry studies:

- 46 patients with stage II-III NSCLC who received induction chemoIO followed by definitive chemoradiation therapy (CRT, 60-66Gy/30 fractions with concurrent platinum-based doublet chemotherapy, n=31) or definitive hypofractionated-RT alone (hypo-RT, 45-60Gy/15-20 fractions without concurrent chemotherapy, n=15). Disease outcomes (OS and PFS) have been published in this cohort and were not different by radiation approach (2)
- 119 patients with upfront unresectable stage II-III NSCLC receiving definitive CRT without prior induction.

Toxicity scoring:

- (1) Binary composite endpoint defined as any of the following within 1 year of RT initiation: *esophagitis* $\geq G3$, *pneumonitis* $\geq G3$, *cardiac events* $\geq G2$ or *lymphopenia* $\geq G4$.
- TTB scoring was applied per (3), assigning severity-weighted domain scores across cardiac events, pneumonitis, lymphopenia, and esophagitis (range 0-340).

Statistical Analysis:

Between-arm comparisons used Fisher's exact test for binary outcomes and Mann-Whitney U test for TTB scores.

REFERENCES & ACKNOWLEDGEMENTS

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Artificial Intelligence (AI) Use Disclaimer

Claude (Anthropic) was used to assist with language editing and with drafting statistical analysis and figure-generation code. All code was executed, and all content was reviewed and verified by the authors. No data or results were generated by AI.

DISCUSSION AND CONCLUSION

- CRT is associated with substantial and consistent toxicity burden across two independent cohorts in distinct clinical settings (induction chemoIO and upfront)
- Composite toxicity after CRT ranged from 45-56% and TTB was higher after CRT compared to definitive hypoRT in both cohorts
- These data support evaluating optimized radiation approaches in locally advanced NSCLC after induction chemoIO.

RESULTS

Table 1. Baseline Characteristics

Characteristic	Post-induction CRT (n=31)	Post-induction definitive hypoRT (n=15)	Upfront unresectable CRT (n=119)	p	p: 1 vs 2	p: 1 vs 3	p: 2 vs 3
Age, years, median [IQR]	66 [61-72]	64 [59-70]	72 [65-77]	0.01	0.51	0.03	0.03
RT dose, cGy, median [IQR]	6600.0 [6300.0-6600.0]	6000.0 [5375.0-6000.0]	6600.0 [6600.0-6600.0]	<0.001	<0.001	0.89	<0.001
Number of fractions, median [IQR]	30 [30-30]	15 [15-15]	30 [30-30]	<0.001	<0.001	0.62	<0.001
Sex				0.54	0.53	1.00	0.29
M	17 (54.8)	6 (40.0)	65 (55.1)				
F	14 (45.2)	9 (60.0)	53 (44.9)				
Radiation modality				0.09	0.07	1.00	0.04
Photon	21 (67.7)	14 (93.3)	78 (65.5)				
Proton	10 (32.3)	1 (6.7)	41 (34.5)				
AJCC stage				0.07	0.33	0.01	0.77
IIA	2 (6.5)	0 (0.0)	9 (7.6)				
IIB	7 (22.6)	2 (13.3)	11 (9.2)				
IIIA	11 (35.5)	6 (40.0)	54 (45.4)				
IIIB	7 (22.6)	7 (46.7)	43 (36.1)				
IIIC	4 (12.9)	0 (0.0)	2 (1.7)				
Histology				0.62	0.41	0.50	0.76
Adenocarcinoma	12 (38.7)	8 (53.3)	58 (49.6)				
Squamous	15 (48.4)	7 (46.7)	49 (41.9)				
Other, NSCLC	4 (12.9)	0 (0.0)	10 (8.5)				
Smoking status				0.37	1.00	0.39	0.19
Never	2 (6.5)	0 (0.0)	17 (15.3)				
Former	22 (71.0)	11 (73.3)	75 (67.6)				
Current	7 (22.6)	4 (26.7)	19 (17.1)				
Induction regimen							
Plat/Tax/Pembro	9 (29.0)	7 (46.7)	-				
Plat/Pem/Pembro	9 (29.0)	7 (46.7)	-				
Plat/Tax/Nivo	9 (29.0)	1 (6.7)	-				
Plat/Pem/Nivo	3 (9.7)	0 (0.0)	-				
Plat/Tax/Nivo/Ipi	1 (3.2)	0 (0.0)	-				

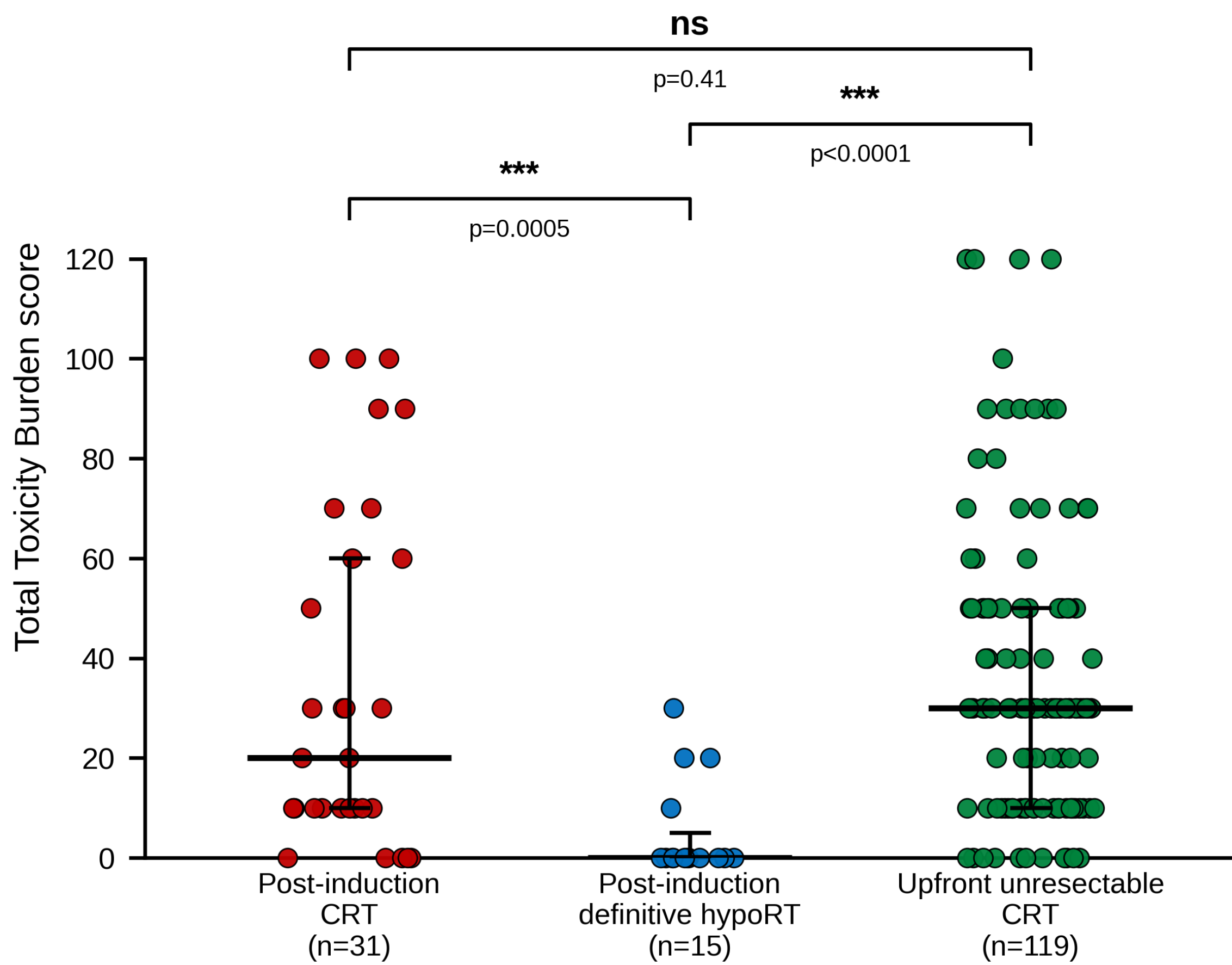


Figure 1. TTB was markedly elevated in the CRT arm (median 20, IQR 10-60; mean 33.5±33.8) versus definitive hypo-RT alone (median 0, IQR 0-5; mean 5.3±9.9; p=0.0005), with pneumonitis and lymphopenia as dominant contributors. The TTB result was robust across six lymphopenia re-weighting sensitivity analyses (all p<0.05) and was not confounded by follow-up time (Spearman r=0.115, p=0.448). In the upfront CRT cohort, TTB was similarly elevated relative to hypo-RT alone (median 30; p<0.001).

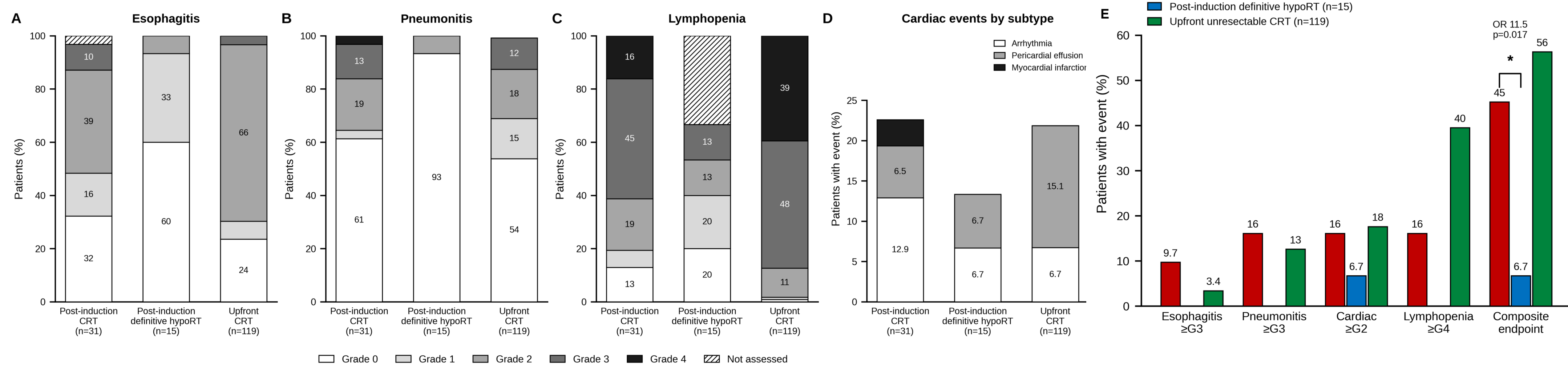


Figure 2. (A-D) Lymphopenia $\geq G4$ was higher in the upfront CRT cohort (39.0% vs 16.1%; p=0.02), potentially reflecting worse baseline performance status or larger radiation field volumes in this population. (E) In the induction chemoIO cohort, the binary composite event rate was significantly higher in the CRT arm versus definitive hypo-RT alone (14/31, 45.2% vs 1/15, 6.7%; p=0.017). In the upfront CRT cohort, the overall composite event rate was 67/119 (56.0%). Except for lymphopenia, neither the binary composite score nor TTB differed significantly between the two CRT cohorts (composite p=0.227; TTB p=0.340)