

Table S1 Univariate logistic regression analysis for severe radiation induced lymphopenia (ALC nadir <200/μL).

Variable	Odds ratio	P value	FDR
Age	1.006	0.712	0.769
Baseline WBC	0.860	0.030	0.052
Baseline Hb	0.771	0.003	0.009
Baseline PLT	0.997	0.056	0.086
Baseline ALC	0.999	0.002	0.007
Baseline ANC	1.000	0.191	0.255
PTV_volume	1.001	0.088	0.124
Beam-on-time	1.000	0.200	0.261
EQD2	0.999	0.024	0.046
Body_V10	1.089	0.001	0.005
Body_V20	1.118	0.006	0.014
Body_V30	1.112	0.031	0.054
Body_V40	1.083	0.183	0.248
Body_V5	1.056	0.005	0.013
Body_V50	1.059	0.468	0.549
Body_V60	0.885	0.315	0.394
EDIC	1.236	0.085	0.123
Esophagus_V10	1.016	0.029	0.052
Esophagus_V20	1.022	0.006	0.014
Esophagus_V30	1.021	0.016	0.032
Esophagus_V40	1.020	0.026	0.048
Esophagus_V5	1.014	0.042	0.072
Esophagus_V50	1.022	0.024	0.046
Esophagus_V60	1.015	0.271	0.348
GreatVessels_V10	1.028	0.010	0.021
GreatVessels_V20	1.027	0.004	0.010
GreatVessels_V30	1.022	0.014	0.029
GreatVessels_V40	1.016	0.083	0.121
GreatVessels_V5	1.036	0.003	0.009
GreatVessels_V50	1.008	0.393	0.479
GreatVessels_V60	0.985	0.288	0.365
Heart_V10	1.015	0.007	0.016
Heart_V20	1.020	0.004	0.012
Heart_V30	1.023	0.014	0.029
Heart_V40	1.023	0.060	0.093
Heart_V5	1.013	0.006	0.014
Heart_V50	1.030	0.075	0.111
Heart_V60	1.024	0.476	0.552
HEDOS_D10	1.346	0.001	0.003
HEDOS_D100	1.449	<0.001	0.002
HEDOS_D15	1.359	0.001	0.002
HEDOS_D2	1.296	0.002	0.006
HEDOS_D20	1.370	<0.001	0.002
HEDOS_D25	1.379	<0.001	0.002
HEDOS_D30	1.387	<0.001	0.002
HEDOS_D35	1.393	<0.001	0.002
HEDOS_D40	1.398	<0.001	0.002
HEDOS_D45	1.404	<0.001	0.002
HEDOS_D5	1.324	0.001	0.004
HEDOS_D50	1.409	<0.001	0.002
HEDOS_D55	1.415	<0.001	0.002
HEDOS_D60	1.419	<0.001	0.002
HEDOS_D65	1.423	<0.001	0.002
HEDOS_D70	1.427	<0.001	0.002
HEDOS_D75	1.431	<0.001	0.002
HEDOS_D80	1.436	<0.001	0.002
HEDOS_D85	1.440	<0.001	0.002
HEDOS_D90	1.445	<0.001	0.002
HEDOS_D95	1.447	<0.001	0.002
HEDOS_mean	1.409	<0.001	0.002
Liver_V10	1.013	0.375	0.463
Liver_V20	0.996	0.895	0.924
Liver_V30	0.996	0.934	0.954
Liver_V40	1.003	0.968	0.968
Liver_V5	1.015	0.150	0.207
Liver_V50	0.981	0.863	0.901
Liver_V60	0.906	0.608	0.664
Lung_V10	1.045	0.000	0.002
Lung_V20	1.060	0.006	0.014
Lung_V30	1.032	0.197	0.260
Lung_V40	1.008	0.776	0.819
Lung_V5	1.032	0.002	0.007
Lung_V50	0.976	0.468	0.549
Lung_V60	0.879	0.011	0.023
Spleen_V10	1.062	0.049	0.080
Spleen_V20	1.079	0.048	0.080
Spleen_V30	1.096	0.052	0.084
Spleen_V40	1.119	0.054	0.086
Spleen_V5	1.039	0.028	0.051
Spleen_V50	1.174	0.065	0.098
Spleen_V60	1.249	0.149	0.207
Vertebrae_V10	1.031	0.002	0.007
Vertebrae_V20	1.031	0.002	0.006
Vertebrae_V30	1.035	0.001	0.002
Vertebrae_V40	1.035	0.001	0.003
Vertebrae_V5	1.036	<0.001	0.002
Vertebrae_V50	1.040	0.006	0.014
Vertebrae_V60	1.015	0.570	0.630

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; Dxx (e.g., HEDOS D100), dose received by xx% of circulating blood; EDIC, effective dose to immune cells; EQD2, equivalent dose in 2 Gy fractions; FDR, false discovery rate; HEDOS, hematological dose; Hb, hemoglobin; PTV, planning target volume; PLT, platelet count; Vx (e.g., Lung V10, Liver V30), percentage; volume of the specified organ receiving ≥x Gy; WBC, white blood cell count.

Table S2 Univariate Cox regression analysis for PFS and OS

Variables	OS			PFS		
	HR (95% CI)	P value	FDR	HR (95% CI)	P value	FDR
Body_V10	1.06 (1.03–1.09)	<0.001	<0.001	1.06 (1.03–1.09)	<0.001	<0.001
Body_V20	1.09 (1.04–1.14)	<0.001	<0.001	1.09 (1.05–1.13)	<0.001	<0.001
Body_V30	1.11 (1.05–1.17)	<0.001	<0.001	1.11 (1.06–1.16)	<0.001	<0.001
Body_V40	1.12 (1.05–1.2)	0.001	0.011	1.13 (1.07–1.20)	<0.001	<0.001
Body_V5	1.04 (1.02–1.06)	0.001	0.011	1.04 (1.02–1.06)	<0.001	<0.001
Body_V50	1.19 (1.09–1.29)	<0.001	<0.001	1.18 (1.09–1.26)	<0.001	<0.001
Body_V60	1.24 (1.10–1.40)	<0.001	<0.001	1.21 (1.09–1.35)	0.001	0.014
Esophagus_V10	1.01 (1.00–1.01)	0.131	0.334	1.00 (1.00–1.01)	0.313	0.753
Esophagus_V20	1.01 (1.00–1.02)	0.073	0.292	1.00 (1.00–1.01)	0.306	0.752
Esophagus_V30	1.01 (1.00–1.02)	0.202	0.362	1.00 (0.99–1.01)	0.514	0.834
Esophagus_V40	1.01 (1.00–1.02)	0.236	0.388	1.00 (0.99–1.01)	0.542	0.834
Esophagus_V5	1.00 (1.00–1.01)	0.200	0.362	1.00 (1.00–1.01)	0.404	0.801
Esophagus_V50	1.01 (0.99–1.02)	0.336	0.459	1.00 (0.99–1.01)	0.734	0.838
Esophagus_V60	1.01 (0.99–1.02)	0.353	0.464	1.00 (0.98–1.01)	0.784	0.849
GreatVessels_V10	1.01 (0.99–1.02)	0.390	0.501	1.01 (1.00–1.02)	0.159	0.529
GreatVessels_V20	1.01 (1.00–1.02)	0.183	0.357	1.00 (1.00–1.01)	0.370	0.801
GreatVessels_V30	1.01 (1.00–1.02)	0.244	0.388	1.00 (0.99–1.01)	0.493	0.834
GreatVessels_V40	1.00 (0.99–1.02)	0.378	0.491	1.00 (1.00–1.01)	0.347	0.800
GreatVessels_V5	1.01 (0.99–1.02)	0.303	0.442	1.01 (1.00–1.02)	0.109	0.440
GreatVessels_V50	1.01 (1.00–1.02)	0.250	0.392	1.01 (1.00–1.02)	0.074	0.409
GreatVessels_V60	1.00 (0.99–1.02)	0.561	0.671	1.01 (1.00–1.02)	0.203	0.588
Heart_V10	1.01 (1.00–1.01)	0.105	0.333	1.00 (1.00–1.01)	0.416	0.810
Heart_V20	1.01 (1.00–1.02)	0.029	0.156	1.00 (0.99–1.01)	0.512	0.834
Heart_V30	1.01 (1.00–1.02)	0.047	0.204	1.00 (0.99–1.01)	0.883	0.899
Heart_V40	1.01 (1.00–1.02)	0.164	0.343	1.00 (0.99–1.02)	0.825	0.863
Heart_V5	1.00 (1.00–1.01)	0.168	0.343	1.00 (1.00–1.01)	0.607	0.834
Heart_V50	1.01 (0.99–1.03)	0.190	0.358	1.01 (0.99–1.03)	0.525	0.834
Heart_V60	1.02 (0.98–1.06)	0.296	0.442	0.99 (0.96–1.03)	0.768	0.843
HEDOS_D10	1.06 (0.97–1.16)	0.206	0.362	1.02 (0.93–1.11)	0.695	0.834
HEDOS_D100	1.11 (1.00–1.23)	0.044	0.199	1.03 (0.93–1.13)	0.612	0.834
HEDOS_D15	1.06 (0.97–1.17)	0.187	0.358	1.02 (0.93–1.11)	0.694	0.834
HEDOS_D2	1.05 (0.96–1.14)	0.285	0.440	1.02 (0.94–1.10)	0.719	0.834
HEDOS_D20	1.07 (0.97–1.17)	0.171	0.343	1.02 (0.93–1.11)	0.686	0.834
HEDOS_D25	1.07 (0.97–1.18)	0.158	0.343	1.02 (0.93–1.12)	0.670	0.834
HEDOS_D30	1.07 (0.98–1.18)	0.148	0.341	1.02 (0.93–1.12)	0.666	0.834
HEDOS_D35	1.08 (0.98–1.18)	0.140	0.341	1.02 (0.93–1.12)	0.660	0.834
HEDOS_D40	1.08 (0.98–1.19)	0.133	0.334	1.02 (0.93–1.12)	0.656	0.834
HEDOS_D45	1.08 (0.98–1.19)	0.127	0.334	1.02 (0.93–1.12)	0.651	0.834
HEDOS_D5	1.06 (0.96–1.15)	0.239	0.388	1.02 (0.93–1.11)	0.717	0.834
HEDOS_D50	1.08 (0.98–1.19)	0.122	0.334	1.02 (0.93–1.12)	0.650	0.834
HEDOS_D55	1.08 (0.98–1.19)	0.117	0.334	1.02 (0.93–1.12)	0.646	0.834
HEDOS_D60	1.08 (0.98–1.19)	0.111	0.334	1.02 (0.93–1.12)	0.647	0.834
HEDOS_D65	1.08 (0.98–1.20)	0.106	0.333	1.02 (0.93–1.13)	0.641	0.834
HEDOS_D70	1.09 (0.98–1.20)	0.100	0.332	1.02 (0.93–1.13)	0.635	0.834
HEDOS_D75	1.09 (0.99–1.20)	0.096	0.329	1.02 (0.93–1.13)	0.635	0.834
HEDOS_D80	1.09 (0.99–1.20)	0.090	0.318	1.02 (0.93–1.13)	0.630	0.834
HEDOS_D85	1.09 (0.99–1.21)	0.085	0.310	1.02 (0.93–1.13)	0.628	0.834
HEDOS_D90	1.09 (0.99–1.21)	0.08	0.301	1.02 (0.93–1.13)	0.626	0.834
HEDOS_D95	1.10 (0.99–1.21)	0.072	0.292	1.03 (0.93–1.13)	0.615	0.834
HEDOS_mean	1.08 (0.98–1.19)	0.125	0.334	1.02 (0.93–1.12)	0.653	0.834
EDIC	1.10 (0.96–1.27)	0.170	0.343	1.07 (0.94–1.22)	0.279	0.701
Liver_V10	1.02 (1.00–1.03)	0.035	0.172	1.01 (1.00–1.03)	0.176	0.552
Liver_V20	1.03 (0.99–1.06)	0.123	0.334	1.02 (0.99–1.05)	0.188	0.559
Liver_V30	1.04 (0.98–1.11)	0.173	0.343	1.04 (0.99–1.10)	0.140	0.510
Liver_V40	1.06 (0.97–1.15)	0.221	0.373	1.06 (0.98–1.15)	0.163	0.529
Liver_V5	1.01 (1.00–1.03)	0.019	0.107	1.01 (0.99–1.02)	0.258	0.663
Liver_V50	1.06 (0.94–1.20)	0.318	0.449	1.07 (0.96–1.19)	0.231	0.639
Liver_V60	1.10 (0.91–1.33)	0.347	0.464	1.08 (0.92–1.27)	0.343	0.800
Lung_V10	1.01 (1.00–1.03)	0.040	0.188	1.01 (1.00–1.02)	0.080	0.409
Lung_V20	1.01 (0.99–1.03)	0.524	0.640	1.02 (1.00–1.04)	0.058	0.377
Lung_V30	1.00 (0.97–1.03)	0.992	0.992	1.02 (1.00–1.05)	0.065	0.387
Lung_V40	1.00 (0.97–1.03)	0.919	0.953	1.03 (1.00–1.06)	0.034	0.240
Lung_V5	1.01 (1.00–1.02)	0.170	0.343	1.01 (1.00–1.02)	0.127	0.493
Lung_V50	1.01 (0.97–1.05)	0.589	0.686	1.04 (1.01–1.07)	0.016	0.139
Lung_V60	0.99 (0.94–1.04)	0.707	0.777	1.04 (0.99–1.09)	0.099	0.414
Spleen_V10	1.02 (1.01–1.04)	0.009	0.057	1.00 (0.98–1.02)	0.751	0.843
Spleen_V20	1.03 (1.01–1.05)	0.007	0.047	1.01 (0.98–1.03)	0.697	0.834
Spleen_V30	1.04 (1.01–1.06)	0.006	0.042	1.01 (0.98–1.04)	0.659	0.834
Spleen_V40	1.04 (1.01–1.07)	0.005	0.040	1.01 (0.97–1.04)	0.628	0.834
Spleen_V5	1.02 (1.01–1.03)	0.006	0.042	1.00 (0.99–1.02)	0.563	0.834
Spleen_V50	1.05 (1.02–1.09)	0.005	0.040	1.01 (0.97–1.06)	0.547	0.834
Spleen_V60	1.10 (1.01–1.21)	0.031	0.159	1.02 (0.93–1.13)	0.671	0.834
Vertebrae_V10	1.01 (1.00–1.02)	0.143	0.341	1.01 (1.00–1.02)	0.015	0.139
Vertebrae_V20	1.01 (1.00–1.02)	0.075	0.292	1.01 (1.00–1.02)	0.016	0.139
Vertebrae_V30	1.01 (1.00–1.02)	0.288	0.440	1.01 (1.00–1.02)	0.028	0.211
Vertebrae_V40	1.01 (0.99–1.02)	0.351	0.464	1.01 (1.00–1.02)	0.060	0.377
Vertebrae_V5	1.01 (1.00–1.02)	0.241	0.388	1.01 (1.00–1.02)	0.024	0.194
Vertebrae_V50	1.01 (0.99–1.02)	0.305	0.442	1.01 (1.00–1.03)	0.092	0.409
Vertebrae_V60	1.01 (0.98–1.04)	0.674	0.754	1.01 (0.99–1.04)	0.367	0.801
PTV	1.00 (1.00–1.00)	<0.001	<0.001	1.00 (1.00–1.00)	<0.001	<0.001
Beam-on-time	1.00 (1.00–1.00)	0.216	0.370	1.00 (1.00–1.00)	0.396	0.801
Age	1.01 (0.99–1.03)	0.337	0.459	0.98 (0.96–0.99)	0.005	0.063
Baseline ALC	1.00 (1.00–1.00)	0.979	0.992	1.00 (1.00–1.00)	0.187	0.559
Baseline ANC	1.00 (1.00–1.00)	0.305	0.442	1.00 (1.00–1.00)	0.789	0.849
Baseline Hb	0.86 (0.77–0.95)	0.003	0.028	0.95 (0.86–1.04)	0.255	0.663
Baseline WBC	1.05 (0.99–1.12)	0.129	0.334	1.00 (0.94–1.07)	0.895	0.903
Baseline PLT	1.00 (1.00–1.00)	0.467	0.580	1.00 (1.00–1.00)	0.700	0.834
Weight	1.00 (0.98–1.01)	0.854	0.902	1.00 (0.98–1.01)	0.593	0.834
Height	1.01 (0.99–1.03)	0.323	0.451	1.01 (0.99–1.02)	0.394	0.801
Chemotherapy_TC vs. others	1.05 (0.75–1.46)	0.791	0.851	1.25 (0.92–1.70)	0.153	0.529
Radiotherapy (IMRT vs. 3D-CRT)	1.10 (0.76–1.59)	0.613	0.700	1.07 (0.78–1.46)	0.681	0.834
Sex	2.58 (1.56–4.28)	<0.001	<0.001	1.18 (0.82–1.70)	0.383	0.801
Smoking (Ex-smoker vs current-smoker)	0.80 (0.56–1.14)	0.208	0.362	0.82 (0.59–1.15)	0.258	0.663
Smoking (Never-smoker vs. current-smoker)	0.48 (0.30–0.76)	0.002	0.021	0.87 (0.60–1.27)	0.473	0.834
Pack year	1.01 (1.00–1.02)	0.001	0.011	1.00 (0.99–1.00)	0.400	0.801
Histology_others vs. ADC	1.20 (0.65–2.22)	0.564	0.671	0.95 (0.55–1.64)	0.856	0.879
Histolo_SqCC vs. ADC	1.28 (0.91–1.79)	0.152	0.343	0.79 (0.58–1.07)	0.131	0.493
ECOG1	0.82 (0.34–2.01)	0.671	0.754	0.46 (0.19–1.13)	0.089	0.409
ECOG2	1.20 (0.29–5.07)	0.801	0.854	0.31 (0.06–1.61)	0.164	0.529
EQD2	1.00 (1.00–1.00)	0.408	0.512	1.00 (1.00–1.00)	0.232	0.639

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ADC, adenocarcinoma; CRT, conformal radiotherapy; Dxx (e.g., HEDOS D100), dose received by xx% of circulating blood; ECOG, Eastern Cooperative Oncology Group; EDIC, effective dose to immune cells; EQD2, equivalent dose in 2 Gy fractions; FDR, false discovery rate; HEDOS, hematological dose; Hb, hemoglobin; IMRT, intensity modulated radiotherapy; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; PLT, platelet; SqCC, squamous cell carcinoma; TC, taxotere and cyclophosphamide; Vx (e.g., Lung V10, Liver V30), percentage volume of the specified organ receiving ≥x Gy; WBC, white blood cells.

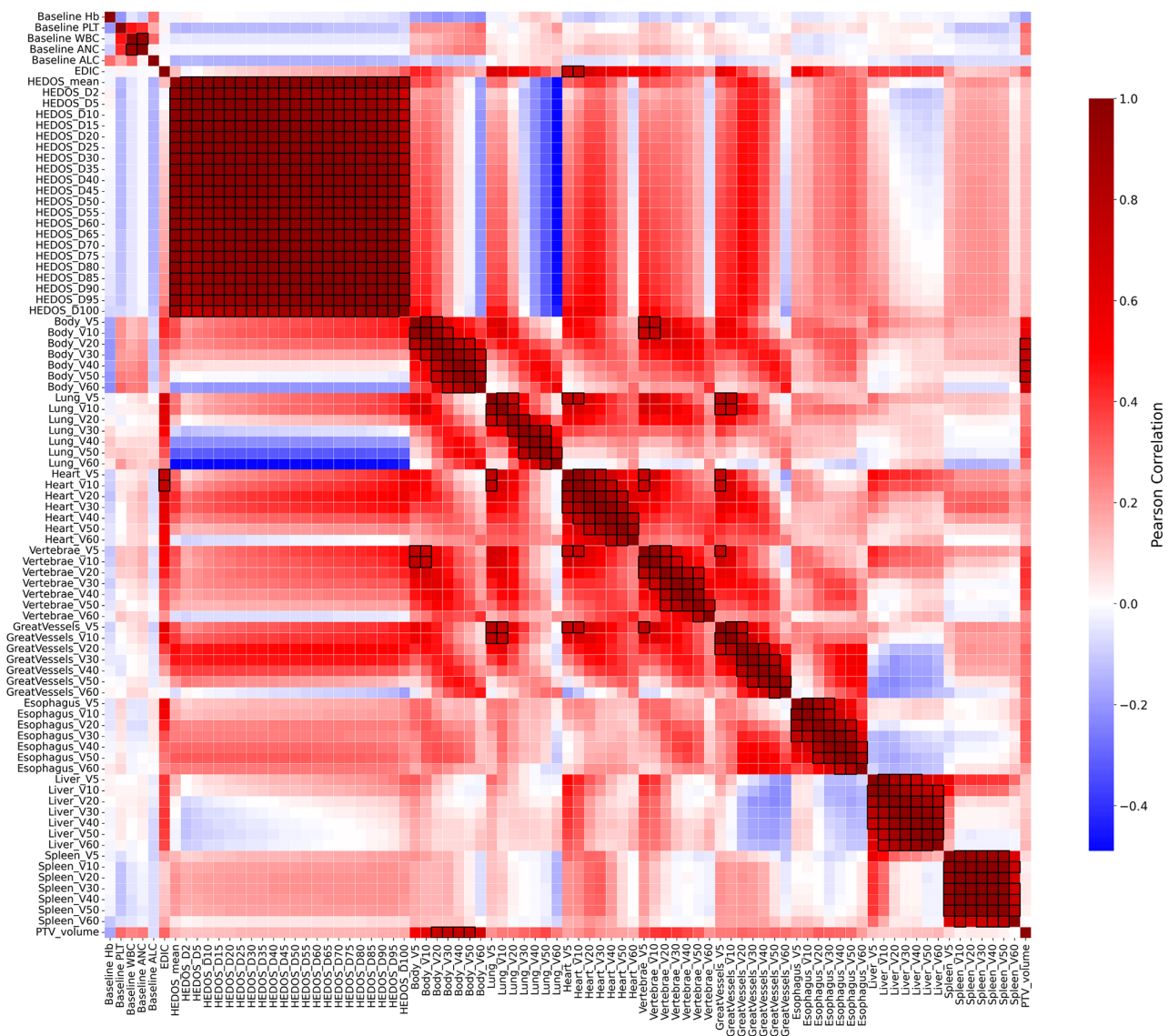


Figure S1 Correlation matrix of dosimetric variables. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; EDIC, effective dose to immune cells; HEDOS, hematological dose; Hb, hemoglobin; PTV, planning target volume; PLT, platelet count; WBC, white blood cell count.

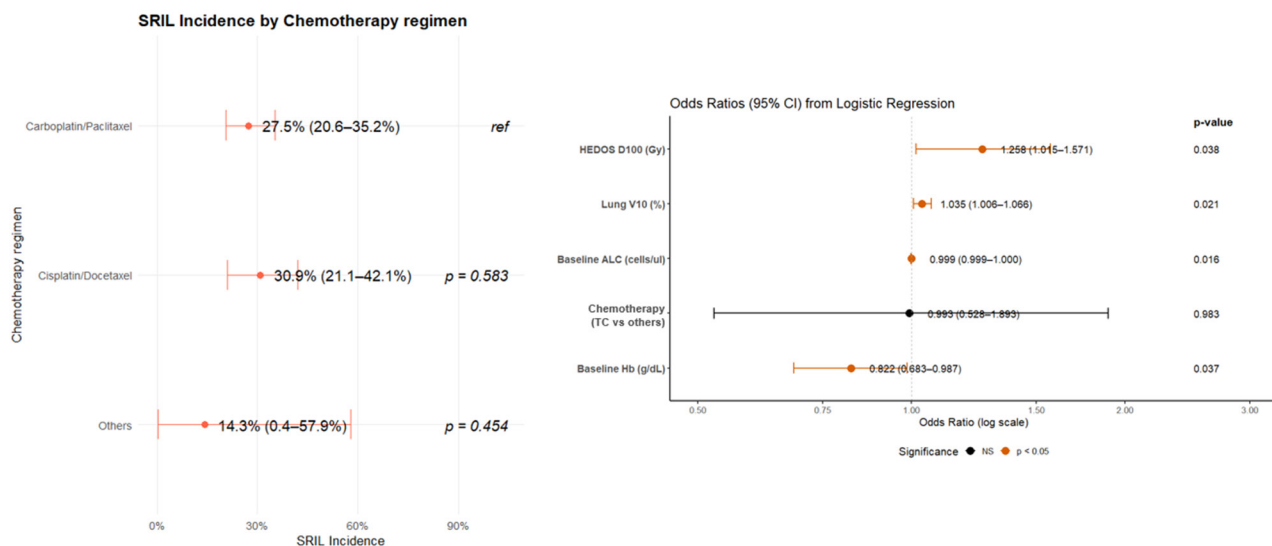


Figure S2 Association between chemotherapy regimens and severe radiation-induced lymphopenia (SRIL, defined as nadir absolute lymphocyte count $<200/\mu\text{L}$). (A) Incidence of SRIL stratified by chemotherapy regimens. (B) Multivariate logistic regression analysis of factors associated with SRIL. Chemotherapy regimen (carboplatin/paclitaxel vs. others) was not significantly associated with SRIL (OR =0.993, $P=0.983$). Dot color indicates statistical significance (orange: $P<0.05$; black: not significant), and horizontal bars represent 95% CIs. ALC, absolute lymphocyte count; CI, confidence interval; Hb, hemoglobin; HEDOS, hematological dose; NS, not significant; OR, odds ratio; SRIL, severe radiation-induced lymphopenia; TC, taxotere and cyclophosphamide.

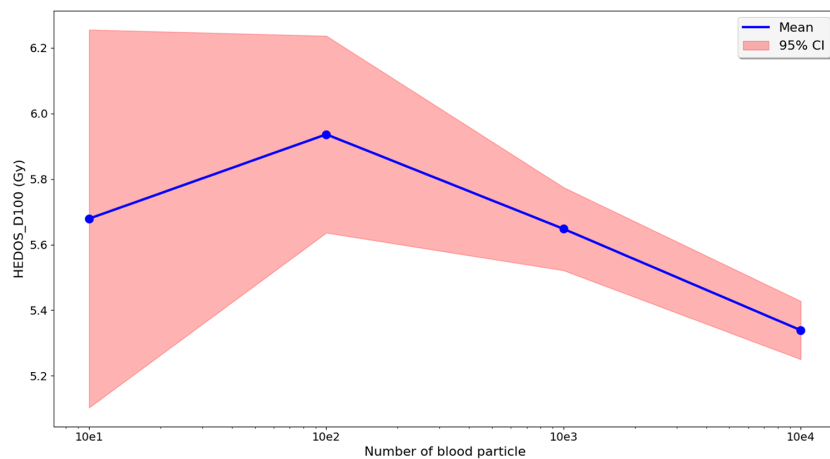


Figure S3 Mean value of minimum hematological dose (HEDOS D100) based on number of blood particles (10^1 – 10^4) calculated from 10 simulations via HEDOS model. Beam-on-time (min) was fixed as 3. Total number of fractions were 33. HEDOS D100 was obtained using same radiotherapy regimen for a patient. CI, confidence interval; HEDOS, hematological dose.