

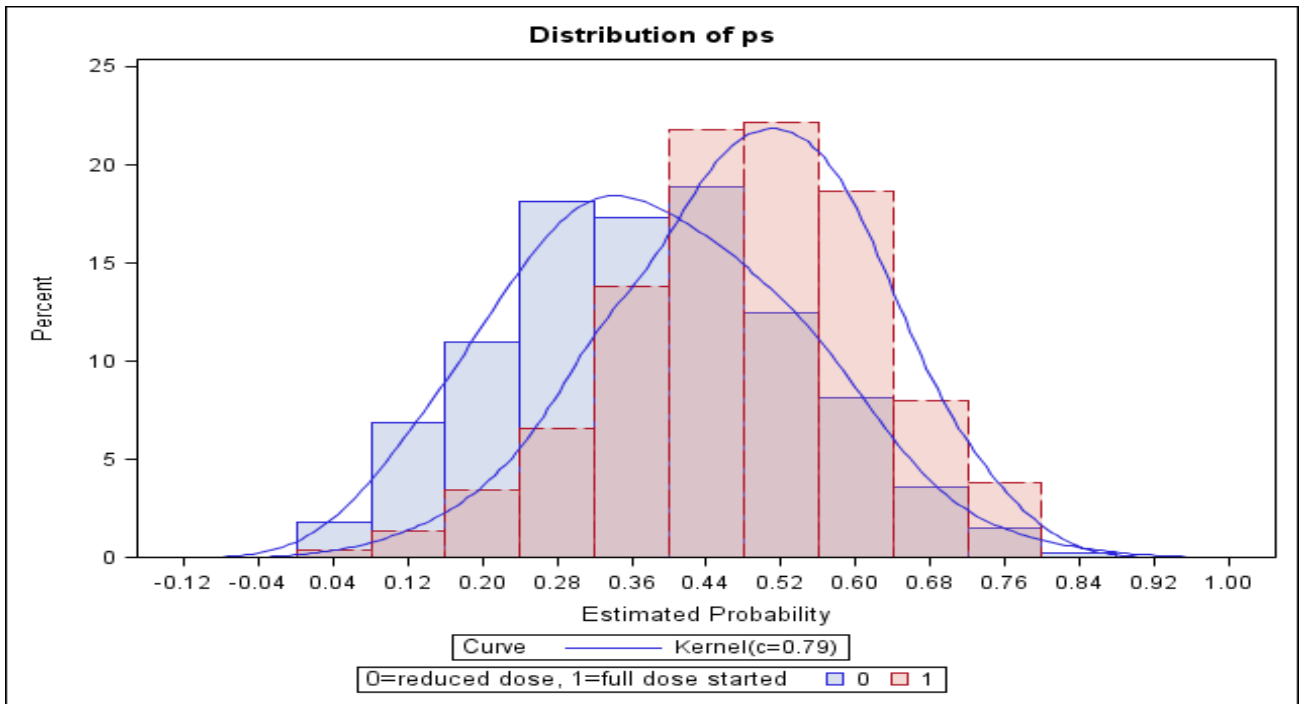
Appendix Table A: Standardized differences of baseline covariates in original and matched sample

Variable	Original sample (n=681)			Matched sample (n=486)		
	Reduced dose N=392	Full dose N=289	Std diff	Reduced dose N=243	Full dose N=243	Std diff
Age	65.5±12.1 66 (58, 74)	62.1±11.1 63 (57, 70)	0.295	62.7±11.8 63 (56, 71)	62.9±10.9 64 (58, 71)	0.016
Female	87 (22.2)	47 (16.3)	0.151	43 (17.7)	44 (18.1%)	0.011
Ethnicity (Other vs rest*)	234 (59.7)	197 (68.2)	0.177	159 (65.4)	159 (65.4)	0.000
Hepatitis B	136 (34.7)	93 (32.2)	0.053	81 (33.3)	78 (32.1)	0.026
Hepatitis C	124 (31.6)	85 (29.4)	0.048	76 (31.3)	73 (30.0)	0.027
Alcohol related	84 (21.4)	75 (26.0)	0.107	62 (25.5)	61 (25.1)	0.009
None Etiology	65 (16.6)	47 (16.3)	0.009	39 (16.1)	42 (17.3)	0.033
Liver cirrhosis	275 (70.2)	205 (70.9)	0.017	170 (70.0)	171 (70.4)	0.009
ECOG PS (0/1 vs rest*)	344 (78.8)	251 (86.9)	0.027	215 (88.5)	207 (85.2)	0.097
Child Pugh (A vs rest*)	330 (84.2)	255 (88.2)	0.118	215 (88.5)	210 (86.4)	0.062
PVT (yes vs rest*)	159 (40.6)	113 (39.1)	0.030	101 (41.6)	94 (38.7)	0.059
T stage (1/2 vs rest*)	139 (35.5)	86 (29.8)	0.122	74 (30.5)	77 (31.7)	0.027
N stage (N0 vs rest*)	263 (67.1)	186 (64.4)	0.058	159 (65.4)	155 (63.8)	0.034
M stage (M0 vs rest*)	200 (51.0)	152 (52.6)	0.032	129 (53.1)	124 (51.0)	0.041
Tumor extension (>50% vs rest*)	113 (28.8)	93 (32.2)	0.073	81 (33.3)	77 (31.7)	0.035
Liver resection	89 (22.7)	74 (25.6)	0.068	63 (25.9)	54 (22.2)	0.087
Tumor ablation	98 (25.0)	50 (17.3)	0.189	47 (19.3)	43 (17.7)	0.042
TACE	156 (39.8)	71 (24.6)	0.330	66 (27.2)	68 (28.0)	0.018
TARE	8 (2.0)	14 (4.8)	0.154	6 (2.5)	11 (4.5)	0.112
SBRT	31 (7.9)	6 (2.1)	0.270	6 (2.5)	6 (2.5)	0.000
Alcohol Injection	15 (3.8)	9 (3.1)	0.039	7 (2.9)	7 (2.9)	0.000
Liver transplant	21 (5.4)	12 (4.2)	0.057	11 (4.5)	10 (4.1)	0.020

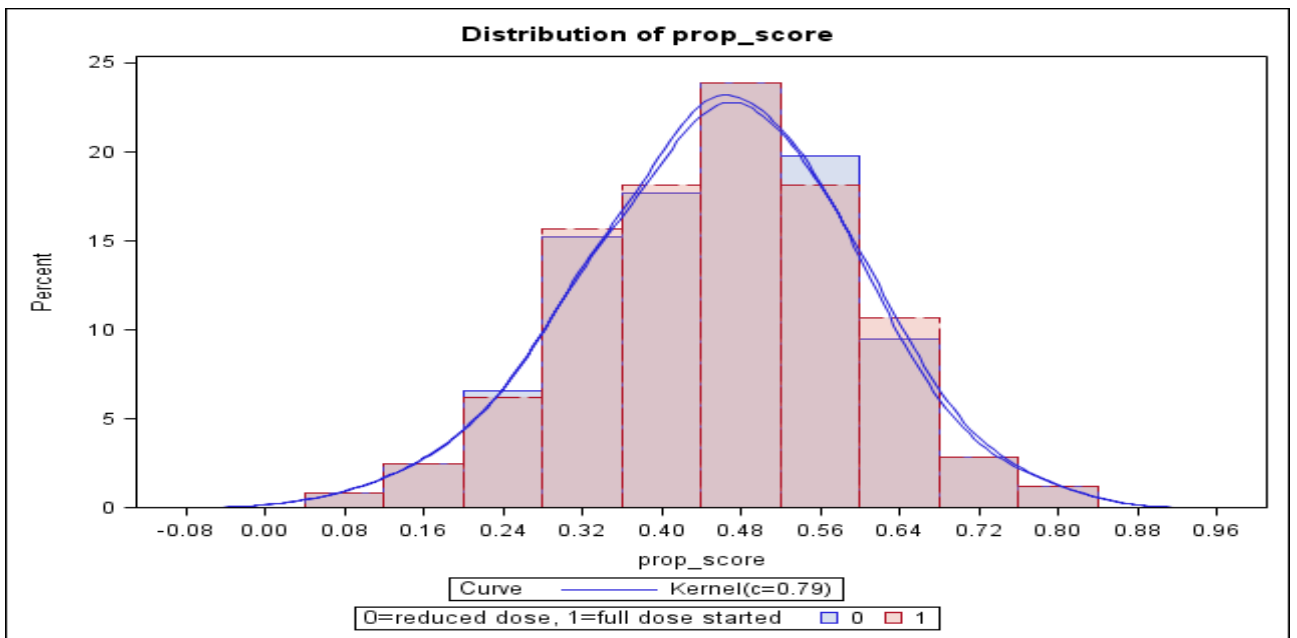
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PVT, portal vein thrombosis; SBRT, stereotactic body radiation; Std diff, Standardized difference; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization;

*Unknown were included under the rest group.

Appendix Figure A.1: Distribution of PS in the original sample before matching



Appendix Figure A.2: Distribution of PS in the matched sample



Appendix Table B: Standardized differences in the weighted IPTW sample

Variable	Std diff
Age	0.0174
Female	0.0146
Ethnicity	0.0116
Hepatitis B	0.0075
Hepatitis C	0.0284
Alcohol related	0.0056
None Etiology	0.0058
Liver cirrhosis	0.0018
ECOG 0/1	0.0003
Child Pugh A	0.0314
PVT (yes)	0.0295
T stage (1/2)	0.0122
N stage (N0)	0.0122
M stage (M0)	0.0162
Tumor extension (>50%)	0.0162
Liver resection	0.0150
Tumor ablation	0.0327
TACE	0.0151
TARE	0.0067
SBRT	0.0454
Alcohol Injection	0.0182
Liver transplant	0.0210

Appendix Table C: Comparison between unadjusted and adjusted weighted IPTW sample

	<50% (n=304)	50-75% (n=163)	>75% (n=214)	Chis q p	IPTW Weigh ted <50%	IPTW Weigh ted 50- 75%	IPTW Weigh ted >75%	IPTW weighted chisq p
Age (median)	65	66	62	<.00 1	64	64	64	0.97
female	64 (21.1)	30 (18.4)	40 (18.7)	0.72	20.4	20.2	21.7	0.91
Ethnicity (other vs rest)	181 (59.5)	107 (65.6)	143 (66.8)	0.18	64.1	61.7	63.8	0.86
Hepatitis B	106 (34.9)	53 (32.5)	70 (32.7)	0.83	33.0	34.1	34.2	0.95
Hepatitis C	99 (32.6)	50 (30.7)	60 (28.0)	0.55	31.4	30.1	31.3	0.96
Alcohol related	55 (18.1)	48 (29.5)	56 (26.2)	0.01	23.2	23.5	23.6	0.99
None Etiology	56 (18.4)	23 (14.1)	33 (15.4)	0.43	16.8	15.8	15.2	0.88
Liver cirrhosis	203 (66.8)	128 (78.5)	149 (69.6)	0.03	69.9	71.5	70.0	0.92
ECGO PS (0/1 vs rest)	257 (84.4)	147 (90.2)	191 (89.3)	0.13	87.3	87.7	87.3	0.99
Child Pugh (A vs rest)	254 (83.6)	143 (87.7)	188 (87.9)	0.29	85.6	86.1	86.0	0.98
PVT (yes vs rest)	118 (38.8)	59 (36.2)	95 (44.4)	0.24	39.5	38.4	41.2	0.85
Tstage (1/2 vs rest)	108 (35.5)	53 (32.5)	64 (29.9)	0.40	32.8	35.6	31.5	0.70
Nstage (N0 vs rest)	207 (68.1)	109 (66.9)	133 (62.2)	0.36	67.4	64.5	66.8	0.81
Mstage (M0 vs rest)	159 (52.3)	92 (56.4)	101 (47.2)	0.20	50.9	50.1	50.1	0.98
Tumor extension (>50% vs rest)	97 (31.9)	45 (27.6)	64 (29.9)	0.62	30.3	28.5	32.6	0.68
Liver resection	76 (25.0)	37 (22.7)	50 (23.4)	0.83	24.1	24.9	23.8	0.96
Tumor ablation	78 (25.7)	33 (20.3)	37 (17.3)	0.07	21.3	22.2	21.6	0.97
TACE	115 (37.8)	57 (35.0)	55 (25.7)	0.01 4	33.2	34.0	32.8	0.97
TARE	6 (2.0)	6 (3.7)	10 (4.7)	0.22	3.7	3.5	3.5	0.99

SBRT	21 (6.9)	9 (5.5)	7 (3.3)	0.20	5.7	5.3	6.5	0.88
Alcohol Injection	12 (4.0)	5 (3.1)	7 (3.3)	0.86	3.1	3.0	2.9	0.99
Liver transplant	1. (4.3)	10 (6.1)	10 (4.7)	0.67	4.4	5.0	4.6	0.96

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PVT, portal vein thrombosis; SBRT, stereotactic body radiation; Std diff, Standardized difference; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization;

Appendix Table D: Observed adverse events

(A) Starting dose

Adverse Event	Dose reduced n (%) N=392	Full dose n (%) N=289	P
Any Toxicity	329 (84%)	257 (89%)	0.063
Hypertension	55 (14%)	40 (14%)	0.944
Fatigue	242 (62%)	191 (66%)	0.243
Rash	106 (27%)	91 (31%)	0.206
Hand-foot syndrome	95 (24%)	102 (35%)	0.002
Headache	11 (3%)	7 (2%)	0.758
Diarrhea	150 (38%)	116 (40%)	0.620
Mucositis	31 (8%)	41 (14%)	0.008
Alopecia	29 (7%)	27 (9%)	0.361
Weight loss	97 (25%)	84 (29%)	0.207
Anorexia	144 (37%)	99 (34%)	0.505

(B) Dose-intensity

Adverse Event	< 50% n (%) N=304	50-75% n (%) N=163	>75 % n (%) N= 214	P
Any Toxicity	242 (80%)	159 (97%)	185 (86%)	<0.001
Hypertension	38 (12%)	28 (17%)	29 (13%)	0.372
Fatigue	177 (58%)	120 (74%)	136 (63%)	0.004
Rash	82 (27%)	60 (37%)	55 (26%)	0.037
Hand-foot syndrome	67 (22%)	77 (47%)	53 (25%)	<0.001
Headache	8 (3%)	8 (5%)	2 (1%)	0.059
Diarrhea	101(33%)	77 (47%)	88 (41%)	0.009
Mucositis	27 (9%)	26 (16%)	19 (9%)	0.038
Alopecia	11 (4%)	24 (15%)	21 (10%)	<0.001
Weight loss	65 (21%)	58 (36%)	58 (27%)	0.004
Anorexia	112 (37%)	63 (39%)	68 (32%)	0.328