

Table S1**Patient characteristics of study cohorts**

Patient characteristics, No. (%)	Group A: First post-RT pEBV DNA <i>undetectable</i>	Group B: First post-RT pEBV DNA <i>detectable and ineligible for randomization</i>	Group C: First post-RT pEBV DNA <i>detectable and eligible for randomization</i>
No. of patients	573	112	104
Median age, years (range)	51.0 (19-80)	52.0 (21-81)	50.5 (20-79)
Sex			
Male	440 (76.8)	81 (72.3)	72 (69.2)
Female	133 (23.2)	31 (27.7)	32 (30.8)
UICC T stage			
T1	135 (23.6)	22 (19.6)	24 (23.1)
T2	137 (23.9)	21 (19.8)	29 (27.9)
T3	220 (38.4)	40 (35.7)	31 (29.8)
T4	81 (14.1)	29 (25.9)	20 (19.2)
UICC N stage			
N0	80 (14.0)	7 (6.3)	10 (9.6)
N1	226 (39.4)	29 (25.9)	41 (39.4)
N2	228 (39.8)	58 (51.8)	37 (35.6)
N3	39 (6.8)	18 (16.1)	16 (15.4)
UICC overall stage			
IIB	170 (29.7)	23 (20.5)	29 (27.9)
III	294 (51.3)	48 (42.9)	39 (37.5)
IVAB	109 (19.0)	41 (36.6)	36 (34.6)
Primary treatment			
RT alone	113 (19.7)	17 (15.2)	16 (15.4)
CRT alone	363 (63.4)	52 (46.4)	66 (63.5)
Neoadjuvant chemotherapy + CRT	97 (16.9)	43 (38.4)	22 (21.1)
First post-RT pEBV DNA (copies/ml)			
Median (IQR)	0 (0-0)	91 (31-871)	44 (18-126)
0	573 (100)	-	-
1-49	-	42 (37.5)	58 (55.8)
50-499	-	37 (33.0)	35 (33.7)
≥500	-	33 (29.5)	11 (10.6)
Timing of first pEBV DNA from last dose of RT, median months (range)	1.5 (0.3-2.6)	1.5 (0.6-2.5)	1.5 (0.3-2.6)
Timing of second pEBV DNA from last dose of RT, median months (range) ^a	NA	NA	8.9 (5.9-11.3)
Timing of first PET-CT from last dose of RT, median months (range)	NA	NA	2.7 (1.8-3.7)
Timing of second PET-CT from last dose of RT, median months (range) ^b	NA	NA	9.5 (5.6-11.4)
Median follow-up, Years (95% C.I.)	6.2 (5.8-6.5)	6.7 (5.7-7.3)	6.6 (6.1-7.2)
Sites of progression			
Any sites	114	62	45
Local only	40	11	10
Regional only	6	2	5
Distant metastasis only	47	35	25
No. of Death	93	53	36

UICC, Union for International Cancer Control (6th Edition); RT, radiotherapy; CRT, chemoradiation; pEBV DNA, plasma Epstein-Barr virus DNA; NA, Not applicable.

^a N=98 (six patients did not complete second pEBV DNA study: three experienced clinical progression, two died of treatment related complications, and one died of intercurrent illness before second plasma EBV DNA)

^b N=97 (seven patients did not complete second PET-CT study: in addition to the same six patient who did not complete the second pEBV DNA, one additional patient experienced clinical progression before second PET-CT).

Table S2**Performance of PET-CT in predicting disease progression.**

Parameters	No. of patients	No. of events	TP (%)	FP (%)	FN (%)	TN (%)	AUC (95% CI)	Sen	Sp	PPV	NPV	Accuracy
Any progression												
Second PET-CT	97	41	30 (31.0)	36 (37.1)	11 (11.3)	20 (20.6)	0.54 (0.43-0.66)	0.73	0.36	0.45	0.65	0.52
Local progression only												
Second PET-CT	97	9	5 (5.2)	47 (48.5)	4 (4.1)	41 (42.2)	0.51 (0.31-0.71)	0.56	0.47	0.10	0.91	0.47
Regional progression only												
Second PET/CT	97	5	3 (3.1)	5 (5.2)	2 (2.1)	87 (89.6)	0.77 (0.51-1.00)	0.60	0.95	0.38	0.98	0.93
Distant metastasis only												
Second PET/CT	97	23	19 (19.6)	9 (9.3)	4 (4.1)	65 (67.0)	0.85 (0.75-0.95)	0.83	0.88	0.68	0.94	0.87

TP, true positive; FP, false positive; FN, false negative; TN, true negative; AUC, area under receiver-operator characteristic curve; C.I. confidence interval; Sen, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

Table S3

Prognostic factors for progression free survival in patients of nasopharyngeal cancer with detectable post-RT pEBV DNA and randomized to adjuvant chemotherapy versus clinical observation (n=97).

Covariates	Univariate analysis		Multivariate analysis ^a	
	Hazard Ratio (95% C.I.)	P value	Hazard Ratio (95% C.I.)	P value
Age (<50, >=50)	1.39 (0.75-2.57)	0.29	-	-
Sex	1.40 (0.72-2.72)	0.33	-	-
UICC T stage (T1/2, T3/4)	2.15 (1.16-4.01)	0.016	-	-
UICC N stage (N0/1, N2/3)	0.88 (0.48-1.60)	0.67	-	-
UICC Overall stage (II/III, IVAB)	1.04 (0.55-1.97)	0.90	-	-
Primary treatment (RT, Chemo-RT)	0.98 (0.45-2.14)	0.96	-	-
Adjuvant chemotherapy (no, yes)	0.84 (0.45-1.53)	0.56	-	-
Post-RT pEBV DNA clearance	9.44 (4.35-20.53)	<0.0001	9.44 (4.35-20.53)	<0.0001
Second post-RT pEBV DNA (0, > 0 copy/ml)				
PET/CT	1.98 (1.00-3.93)	0.051	-	-
Second PET/CT (negative, positive)				

C.I, confidence interval; UICC, Union for International Cancer Control (7th Edition); Chemo, chemotherapy; RT, radiotherapy; pEBV DNA, plasma Epstein-Barr virus DNA.

^a For multivariate analysis, all prognostic factors will be included. By using stepwise selection with the alpha level for the stay in and out of the model as 0.05, the final multivariate model will retain the significant factors with p-value less than 0.05.

Table S4

Sensitivity analysis of post-radiotherapy plasma EBV DNA and long-term survival in nasopharyngeal cancer

	Patient No.	5-year PFS, %	HR (95% C.I.)	P values	5-year OS, %	HR (95% C.I.)	P values	5-year LRFS, %	HR (95% C.I.)	P values	5-year DMFS, %	HR (95% C.I.)	P values
Second post-RT pEBV DNA													
Group C: randomized and completed second pEBV DNA¹	98	55.3	NA	-	68.9	NA	-	60.3	NA	-	64.1	NA	-
pEBV DNA clearance	50	85.5	Reference	-	95.8	Reference	-	85.5	Reference	-	95.8	Reference	-
pEBV DNA non-clearance	48	23.3	9.6 (4.4-20.9)	<0.0001	38.8	15.7 (4.7-51.8)	<0.0001	32.3	6.7 (3.1-14.7)	<0.0001	29.9	20.2 (6.2-66.4)	<0.0001
Case 1 (best case scenario): assume all six drop out patients have pEBV DNA clearance													
pEBV DNA clearance	56	76.3	Reference	-	87.3	Reference	-	76.3	Reference	-	87.3	Reference	-
pEBV DNA non-clearance	48	23.3	5.2 (2.8-9.8)	<0.0001	38.8	5.6 (2.5-12.4)	<0.0001	32.3	3.7 (1.9-6.9)	<0.0001	29.9	7.2 (3.3-15.8)	<0.0001
Case 2 (worst case scenario): assume all six drop out patients have pEBV DNA non-clearance													
pEBV DNA clearance	50	85.5	Reference	-	95.8	Reference	-	85.5	Reference	-	95.8	Reference	-
pEBV DNA non-clearance	54	20.7	10.4 (4.8-22.4)	<0.0001	36.7	16.8 (5.1-55.0)	<0.0001	28.7	7.5 (3.5-16.2)	<0.0001	28.6	21.0 (6.4-68.5)	<0.0001
Case 3 (most likely scenario): assume three patients with clinical progression have pEBV DNA non-clearance and three patients died of treatment complication or intercurrent illness have pEBV DNA clearance													
pEBV DNA clearance	53	80.6	Reference	-	90.4	Reference	-	80.6	Reference	-	90.4	Reference	-
pEBV DNA non-clearance	51	22.0	7.0 (3.6-13.8)	<0.0001	38.8	7.6 (3.1-18.4)	<0.0001	30.4	5.0 (2.5-10.0)	<0.0001	30.3	9.6 (4.0-23.4)	<0.0001

PFS, progression free survival; OS, overall survival; LRFS, locoregional failure free survival; DMFS, distant metastasis free survival; HR, hazard ratio; C.I. confidence interval; RT, radiotherapy; pEBV DNA, plasma Epstein-Barr virus DNA.

¹ N=98 (six patients did not complete second pEBV DNA study: three experienced clinical progression, two died of treatment related complications, and one died of intercurrent illness before second plasma EBV DNA)