Table S1. Patient demographic and clinical characteristics by cohort.

Characteristics	Non-endemic region (*n*=3052)	Endemic region (*n*=3263)			Overall (*N*=6315)	*P* value
	NCC cohort, % (*n*=3052)	Guangzhou cohort, % (*n*=1996)	Sichuan cohort, % (*n*=717)	Hunan cohort, % (*n*=550)		
Sex						0.482
Male	2256 (73.9)	1500 (75.2)	533 (74.3)	396 (72.0)	4685 (74.2)	
Female	796 (26.1)	496 (24.8)	184 (25.7)	154 (28.0)	1630 (25.8)	
Age (years)						<0.001
<48	1487 (48.7)	1141 (57.2)	325 (45.3)	228 (41.5)	3181 (50.4)	
≥48	1565 (51.3)	855 (42.8)	392 (54.7)	322 (58.5)	3134 (49.6)	
KPS score						<0.001
≥80	2966 (97.2)	1862 (93.3)	700 (97.6)	548 (99.6)	6076 (96.2)	
< 80	86 (2.8)	134 (6.7)	17 (2.4)	2 (0.4)	239 (3.8)	
Pathology						<0.001
WHO II	677 (22.2)	72 (3.6)	147 (20.5)	73 (13.3)	969 (15.3)	
WHO III	2214 (72.5)	1924 (96.4)	543 (75.7)	477 (86.7)	5158 (81.7)	
Other	161 (5.3)	0 (0)	27 (3.8)	0 (0)	188 (3.0)	
AJCC 8th T stage						<0.001
T1	428 (14.0)	228 (11.4)	74 (10.3)	86 (15.6)	816 (12.9)	
T2	468 (15.3)	335 (16.8)	98 (13.7)	116 (21.1)	1017 (16.1)	
T3	1306 (42.8)	1003 (50.3)	352 (49.1)	224 (40.7)	2885 (45.7)	
T4	850 (27.9)	430 (21.5)	193 (26.9)	124 (22.5)	1597 (25.3)	
AJCC 8th N stage						<0.001
N0	268 (8.8)	399 (20.0)	58 (8.1)	19 (3.5)	744 (11.8)	
N1	990 (32.4)	741 (37.1)	243 (33.9)	215 (39.1)	2189 (34.7)	
N2	1230 (40.3)	688 (34.5)	288 (40.2)	198 (36.0)	2404 (38.1)	
N3	564 (18.5)	168 (8.4)	128 (17.9)	118 (21.5)	978 (15.5)	
AJCC 8th clinical stage						<0.001
I	57 (1.9)	119 (6.0)	10 (1.4)	2 (0.4)	188 (3.0)	
II	336 (11.0)	226 (11.3)	64 (8.9)	97 (17.6)	723 (11.4)	
III	1374 (45.0)	1086 (54.4)	351 (49.0)	234 (42.5)	3045 (48.2)	
IVA	1285 (42.1)	565 (28.3)	292 (40.7)	217 (39.5)	2359 (37.4)	
EBV DNA (copies/mL)						<0.001
<2000	2766 (90.6)	992 (49.7)	623 (86.9)	443 (80.5)	4824 (76.4)	
2000-20000	229 (7.5)	547 (27.4)	85 (11.9)	81 (14.7)	942 (14.9)	
>20000	57 (1.9)	457 (22.9)	9 (1.3)	26 (4.7)	549 (8.7)	
LDH (U/L)						<0.001
<240	2853 (93.5)	1539 (77.1)	688 (96.0)	524 (95.3)	5604 (88.7)	
≥240	199 (6.5)	457 (22.9)	29 (4.0)	26 (4.7)	711 (11.3)	
Treatment modality						<0.001
CCRT	1476 (48.4)	1084 (54.3)	263 (36.7)	12 (2.2)	2835 (44.9)	
IMRT	845 (27.7)	305 (15.3)	174 (24.3)	9 (1.6)	1333 (21.1)	
IC+CCRT	516 (16.9)	552 (27.7)	201 (28.0)	325 (59.1)	1594 (25.2)	
IC+IMRT	135 (4.4)	0 (0)	35 (4.9)	64 (11.6)	234 (3.7)	
CCRT+AC	60 (2.0)	55 (2.8)	20 (2.8)	0 (0)	135 (2.1)	
IC+CCRT+AC	8 (0.3)	0 (0)	18 (2.5)	119 (21.6)	145 (2.3)	
IMRT+AC	8 (0.3)	0 (0)	5 (0.7)	0 (0)	13 (0.2)	

IC+IMRT+AC	4 (0.1)	0 (0)	1 (0.1)	21 (3.8)	26 (0.4)

Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; EBV DNA, Epstein-Barr virus DNA; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; NCC, national cancer center; OS, overall survival; SMR, standardized mortality ratio.

Table S2. Loss of lifetime for patients in the whole cohort: patients achieving PFS24 and patients not achieving PFS24.

Characteristics	All patients	Patients achieving PFS24 (95% CI)	Patients not achieving PFS24 (95% CI)
All patients	1.09 (0.97, 1.20)	0.01 (-0.08, 0.10)	6.48 (6.09, 6.82)
Sex			
Male	1.12 (0.98, 1.26)	-0.02 (-0.12, 0.09)	6.57 (6.12, 6.94)
Female	0.90 (0.69, 1.11)	0.09 (-0.07, 0.24)	6.13 (5.27, 6.83)
Age (years)			
<48	1.15 (1.00, 1.30)	0.24 (-0.14, 0.34)	6.33 (5.73, 6.83)
≥48	1.02 (0.83, 1.20)	-0.18 (-0.33, 0.03)	6.57 (6.00, 7.01)
KPS score			
≥80	1.06 (0.94, 1.18)	0.01 (-0.08, 0.09)	6.44 (6.05, 6.79)
< 80	1.29 (0.52, 1.99)	-0.05 (-0.65, 0.49)	5.27 (3.46, 6.41)
Pathology			
WHO II	1.51 (1.21, 1.80)	0.08 (-0.12, 0.27)	6.89 (6.09, 7.50)
WHO III	0.99 (0.86, 1.12)	0.03 (-0.07, 0.13)	6.37 (5.90, 6.77)
Other	1.18 (0.41, 1.88)	-0.42 (-0.82, 0)	4.84 (3.05, 6.06)
AJCC 8th T stage			
1	0.45 (0.19, 0.71)	-0.13 (-0.33, 0)	5.62 (4.20, 6.68)
2	0.62 (0.37, 0.86)	-0.16 (-0.33, 0)	5.80 (4.51, 6.73)
3	0.75 (0.59, 0.91)	-0.18 (-0.29, 0)	6.21 (5.48, 6.76)
4	2.28 (2.00, 2.56)	0.65 (0.41, 0.88)	7.24 (6.66, 7.70)
AJCC 8th N stage			
0	0.10 (-0.20, 0.39)	-0.35 (-0.59, -0.12)	7.22 (4.49, 8.21)
1	0.67 (0.48, 0.85)	-0.02 (-0.17, 0.12)	6.07 (5.16, 6.74)
2	1.25 (1.06, 1.44)	0.10 (-0.04, 0.24)	6.42 (5.82, 6.93)
3	2.37 (2.01, 2.71)	0.38 (0.10, 0.64)	6.81 (6.09, 7.38)
AJCC 8th clinical stage			
I	-0.37 (-0.74, 0.01)	-0.26 (-0.72, 0.19)	4.64 (-0.23, 8.29)
II	0.29 (0.01, 0.55)	-0.13 (-0.36, 0.09)	5.23 (3.31, 6.56)
III	0.46 (0.32, 0.60)	-0.23 (-0.32, -0.13)	5.65 (4.91, 6.26)
IVA	2.24 (2.01, 2.47)	0.51 (0.32, 0.69)	7.09 (6.63, 7.48)
EBV DNA (copies/mL)			
<2000	1.00 (0.87, 1.13)	0.00 (-0.09, 0.10)	6.52 (6.08, 6.90)
2000-20000	1.31 (0.90, 1.70)	0.22 (-0.15, 0.56)	4.66 (3.81, 5.34)
>20000	1.75 (1.16, 2.29)	0.08 (-0.30, 0.45)	4.52 (3.47, 5.26)
LDH (U/L)			
<240	0.98 (0.85, 1.10)	0.02 (-0.07, 0.11)	6.32 (5.90, 6.69)
≥240	2.04 (1.58, 2.46)	0.14 (-0.20, 0.46)	7.29 (6.24, 8.00)
Treatment modality			
IMRT	0.61 (0.38, 0.84)	-0.36 (-0.52, -0.20)	6.20 (5.36, 6.85)
CCRT	1.15 (0.98, 1.31)	0.14 (-0.02, 0.25)	6.84 (6.25, 7.32)

IC+IMRT	2.18 (1.34, 2.92)	0.83 (-0.07, 1.51)	5.12 (3.54, 6.19)
IC+CCRT	1.35 (1.03, 1.66)	0.20 (-0.07, 0.45)	5.31 (4.57, 5.90)
IMRT+AC	1.81 (-0.15, 3.64)	0.48 (-0.06, 1.04)	3.98 (-0.08, 5.60)
CCRT+AC	1.38 (0.74, 1.98)	-0.03 (-0.20, 0.17)	5.44 (3.48, 6.70)
IC+IMRT+AC	0.23 (-0.15, 0.95)	-0.16 (-0.16, -0.16)	3.22 (-0.02, 6.80)
IC+CCRT+AC	0.53 (0.08, 0.97)	0.00 (-0.15, 0.18)	1.73 (0.34, 2.92)

Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBV DNA, Epstein-Barr virus DNA; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; PFS24, progression-free status at 24 months post initial treatment.

Table S3. Univariable and multivariable analysis of PFS in patients achieving PFS24 (*n* = 5304).

Characteristics	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex				/	/	/
Male	Ref					
Female	0.89	0.73 - 1.08	0.238			
Age (years)						
<48	Ref			Ref		
≥48	1.58	1.33 - 1.88	<0.001	1.66	1.40-1.98	<0.001
Pathology			0.066	/	/	/
WHO II	Ref					
WHO III	0.79	0.64 - 0.97	0.023			
Other	0.72	0.40 - 1.30	0.278			
AJCC 8th T stage			<0.001			<0.001
1	Ref			Ref		
2	1.02	0.73 - 1.43	0.917	1.03	0.74-1.45	0.853
3	1.05	0.79 - 1.39	0.747	1.09	0.81-1.46	0.575
4	2.33	1.76 - 3.09	<0.001	2.45	1.82-3.29	<0.001
AJCC 8th N stage			<0.001			<0.001
0	Ref			Ref		
1	1.25	0.91 - 1.72	0.164	1.31	0.95-1.80	0.098
2	1.46	1.07 - 2.00	0.016	1.61	1.17-2.22	0.003
3	2.13	1.51 - 3.00	<0.001	2.37	1.63-3.43	<0.001
EBV DNA (copies/mL)			0.007			0.041
<2000	Ref			Ref		
2000-20000	**1.10**	0.84 - 1.45	0.492	1.02	0.77-1.35	0.560
>20000	1.67	1.21 - 2.29	0.002	1.70	1.04-2.79	0.034
LDH (U/L)						
<240	Ref			Ref		
≥240	1.35	1.02 - 1.80	0.037	0.87	0.56-1.35	0.519
Treatment modalities			<0.001			<0.001
CCRT	Ref			Ref		
IMRT	1.06	0.86 - 1.30	0.603	1.34	1.07-1.67	0.011
IC+CCRT	1.31	1.04 - 1.65	0.022	1.04	0.81-1.33	0.757

IC+IMRT	2.17	1.47 - 3.21	<0.001	1.75	1.17-2.62	0.006
CCRT+AC	0.98	0.50 - 1.91	0.957	0.80	0.41-1.56	0.511
IC+CCRT+AC	0.90	0.37 - 2.18	0.810	0.73	0.30-1.78	0.483
IMRT+AC	7.05	2.90 - 17.10	<0.001	6.74	2.76-16.48	<0.001
IC+IMRT+AC	0.94	0.13 - 6.69	0.948	1.73	0.43-7.01	0.441

Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBV DNA, Epstein-Barr Virus DNA; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; LDH, lactate dehydrogenase; OS, overall survival; Ref, reference; SMR, standardized mortality ratio.

Table S4. Univariable and multivariable analysis of sOS in patients achieving PFS24 (*n* = 5304).

Characteristics	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex				/	/	/
Male	Ref					
Female	0.80	0.62 - 1.03	0.087			
Age (years)						
<48	Ref			Ref		
≥48	2.35	1.86 - 2.96	<0.001	2.41	1.90 - 3.04	<0.001
Pathology			0.260	/	/	/
WHO II	Ref					
WHO III	0.84	0.64 - 1.09	0.178			
Other	0.59	0.26 - 1.36	0.216			
AJCC 8th T stage			<0.001			<0.001
1	Ref			Ref		
2	0.96	0.62 - 1.47	0.842	1.02	0.67 - 1.57	0.916
3	0.91	0.63 - 1.32	0.614	0.99	0.68 - 1.44	0.952
4	2.75	1.93 - 3.90	<0.001	3.06	2.12 - 4.42	<0.001
AJCC 8th N stage			0.090	/	/	/
0	Ref					
1	1.09	0.75 - 1.60	0.650			
2	1.15	0.79 - 1.68	0.456			
3	1.59	1.04 - 2.44	0.032			
EBV DNA (copies/mL)			0.685	/	/	/
<2000	Ref					
2000-20000	1.17	0.82 - 1.68	0.385			
>20000	1.01	0.59 - 1.74	0.959			
LDH (U/L)				/	/	/
<240	Ref					
≥240	1.14	0.77 - 1.71	0.513			
Treatment modalities			0.002			0.002
CCRT	Ref			Ref		
IMRT	1.07	0.83 - 1.38	0.590	1.21	0.93 - 1.58	0.158
IC+CCRT	1.01	0.72 - 1.42	0.950	0.97	0.69 - 1.36	0.870

IC+IMRT	2.47	1.53 - 3.98	<0.001	2.32	1.44 - 3.75	0.001
CCRT+AC	0.56	0.18 - 1.74	0.314	0.52	0.16 - 1.62	0.256
IC+CCRT+AC	1.21	0.38 - 3.82	0.745	1.30	0.41 - 4.09	0.659
IMRT+AC	4.89	1.56 - 15.35	0.007	5.27	1.67 - 16.64	0.005
IC+IMRT+AC	0.00	0.00 - 4.59E+79	0.931	0.00	0.00 - 1.90E+113	0.946

Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBV DNA, Epstein-Barr Virus DNA; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; LDH, lactate dehydrogenase; OS, overall survival; Ref, reference; SMR, standardized mortality ratio.

Supplementary Figures

Figure S1

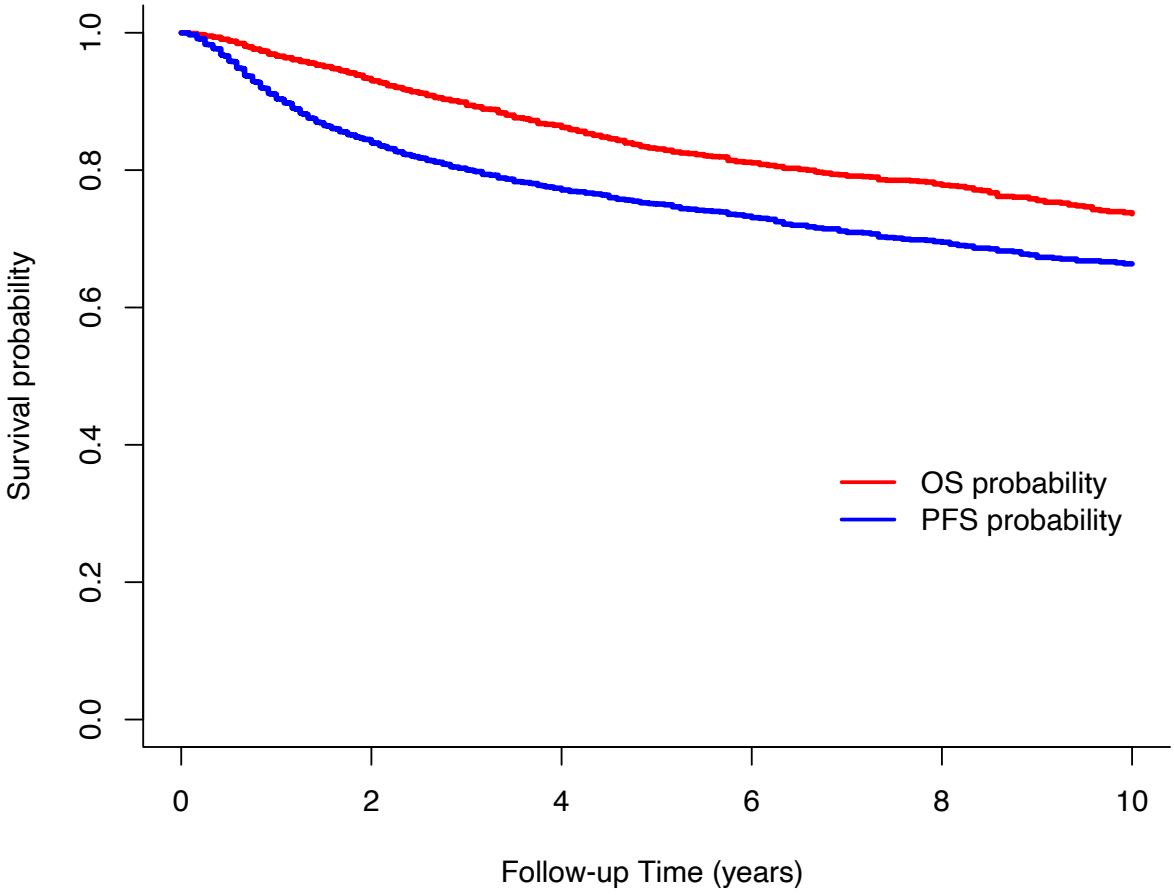

Figure S1. Survival curves for OS and PFS in the entire cohort. OS, overall survival; PFS, progression-free survival.

Figure S2

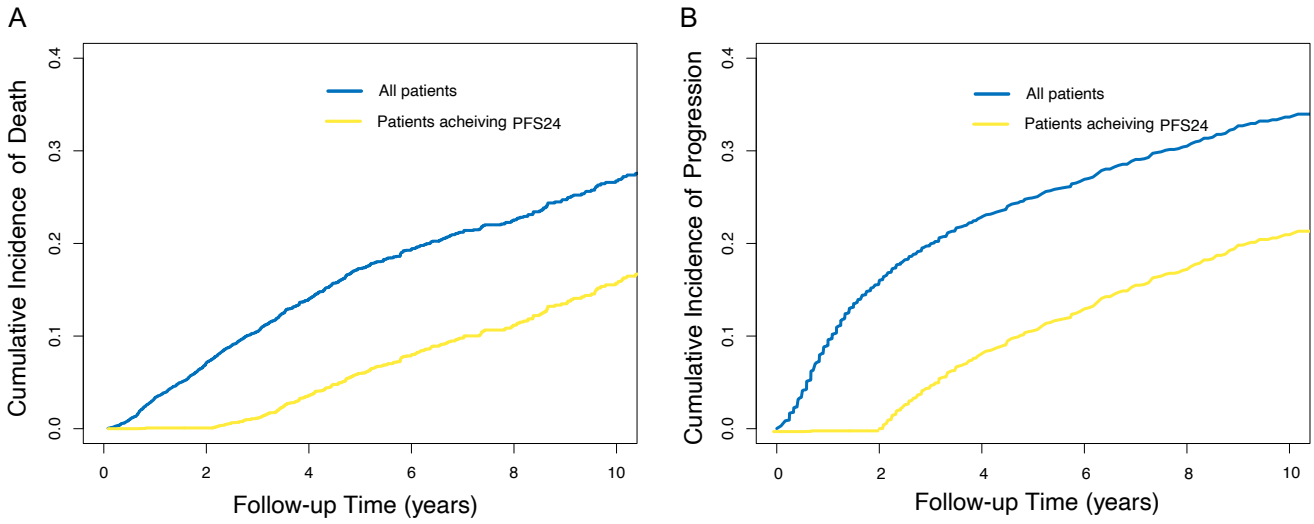

Figure S2. Event-specific cumulative incidences for NPC patients in the entire cohort compared with patients achieving PFS24. (A) Cumulative risk of death and (B) cumulative risk of progression. NPC, nasopharyngeal carcinoma; PFS24, 24-month progression-free survival following initial treatment.