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Original Article

Survival impact of radiotherapy interruption in nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: A big-data intelligence platform-based analysis

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ABSTRACT

Purpose: To evaluate the effect of radiotherapy interruption (RTI) in patients with nasopharyngeal carcinoma (NPC) receiving intensity-modulated radiotherapy (IMRT).

Patients and methods: A total of 7826 patients using the well-established big-data intelligence platform were identified. Computer-generated random numbers were used to assign these patients into a training cohort ($n = 3913$ patients) and an internal validation cohort ($n = 3913$ patients). RTI was defined as the difference between radiation treatment time and planned radiation time (assuming a Monday start). Survival analysis was performed using the Kaplan–Meier method for survival, and log-rank test to evaluate difference. Optimal RTI threshold was identified using the recursive partitioning analyses (RPAs). Multivariate analysis was performed using the Weibull model. The primary endpoint was overall survival (OS).

Results: The optimal threshold of RTI with respect to OS in the training cohort was 6.5 d based on RPAs. Therefore, a uniform threshold of 7 d (<7 vs. ≥7 d) was selected to classify both training and validation cohorts into high and low RTI groups for survival analysis. RTI of ≥7 d showed significant detrimental effects on OS in both training (5-y OS, 82.4% vs 86.5%; $P = 0.001$) and validation cohorts (5-y OS, 85.2% vs 86.7%; $P = 0.013$) than those patients with RTI of <7 d. Consistent with results of the univariate analysis, RTI of ≥7 d was found to be an independent unfavorable prognostic factor for OS in both training (HR, 1.49; 95% CI, 1.14–1.95; $P = 0.003$) and validation cohort (HR, 1.37; 95% CI, 1.07–1.65; $P = 0.031$). Subgroup analysis showed that RTI of ≥7 d had significant adverse effects on prognosis of NPC patients receiving IMRT, regardless of TNM stage and chemotherapy ($P < 0.05$ for all).

Conclusions: In the IMRT era, RTI independently influences survival. Raising RTI ≥ 7 d was consistently unfavorable for NPC survival. Medical practitioners must remind patients on the importance of minimizing RT interruptions.

Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiotherapy; RTI, radiotherapy interruption; RTT, radiotherapy treatment time; 2DRT, two-dimensional RT; OS, overall survival; DFS, disease-free survival; IMRT, intensity-modulated radiotherapy; RPAs, recursive partitioning analyses; HRs, hazard ratios; SYSUCC, Sun Yat-Sen University Cancer Centre; MRI, magnetic resonance imaging; CT, computed tomography; PET-CT, 18F-fluorodeoxyglucose positron emission tomography and computed tomography; AJCC, American Joint Commission on Cancer; PTV, planning target volume; GTVnx, primary gross tumor volume; GTVnd, gross tumor volume in the involved lymph nodes; CTV1, high-risk clinical target volume; CTV2, low-risk clinical target volume; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; RDD, Research Data Deposit public platform; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; WHO, World Health Organization; IQR, interquartile range.

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Nasopharyngeal carcinoma (NPC) is an endemic malignancy in southern China [1,2]. Currently, radiotherapy (RT) is the foundation of radical treatment technique for NPC patients [3]. Radiotherapy interruption (RTI) often occurs because of severe acute treatment-related toxicity, machinery malfunctions, limited medical resources, and public holidays. Additionally, RTI and prolonged radiotherapy treatment time (RTT) were found to be associated with inferior prognosis of NPC patients treated by two-dimensional RT (2DRT) [4–6].

Intensity-modulated radiotherapy (IMRT) over the past two decades has steadily replaced 2DRT as the main course of RT, due to improved tumor target coverage and organs-at-risk sparing [7]. However, the role of RTI remains controversial in the IMRT era. Presently, only five studies have evaluated the effects of RTI in NPC patients receiving IMRT [8–12]. Of these studies, two [8,9] reported RTI was associated with inferior survival outcomes. In contrast, the other three studies failed to observe an association between RTI and survival outcomes [10–12]. Given the lack of studies, the effects of RTI on survival remains unclear in the IMRT era. Moreover, whether there is an optimal threshold beyond which elevated RTI adversely affects NPC prognosis warrants further examination.

To fill this current gap in knowledge, we conceived and initiated a large-scale, real-world study to estimate the prognostic value of RTI on overall survival (OS) and disease-free survival (DFS) of NPC in the IMRT era.

Patients and methods

Data extraction

The NPC-specific database from the well-established big-data intelligence platform at Sun Yat-Sen University Cancer Centre (SYSUCC) was adopted to identify patients with histologically proven, non-disseminated NPC diagnosed between April 2009 and December 2015. Patients' demographic, diagnostic, and therapeutic information were obtained from the big-data intelligence platform using search terms, such as "diagnosis", "histology type", "age at diagnosis", "sex", "RT technology", "TNM stage", "prescribed fractions", "RT of initiation and completion time", and "regimens of chemotherapy". A detailed description of the intelligence platform at SYSUCC is presented in our previously published study [13]. Briefly, the novel "big data" research system enables organizing, integrating, and updating real-time data automatically from numerous clinical business systems.

Study population and treatment

The study cohort comprised of 7826 NPC patients from SYSUCC with histologically confirmed NPC after radical IMRT. Computer-generated random numbers were used to assign these patients into a training cohort consisting of 3913 patients and an internal validation cohort of 3913 patients. All patients completed a pretreatment evaluation, including a complete patient history, physical examination, hematology and biochemistry profiling, fiberoptic nasopharyngoscopy, neck and nasopharyngeal magnetic resonance imaging (MRI), abdominal ultrasonography, whole body bone scan, computed tomography (CT), or 18F-Fluorodeoxyglucose positron emission tomography and CT (PET-CT). All patients were restaged according to the 8th edition of the American Joint Commission on Cancer staging system [14]. The present study received approval from the Institutional Review Board at SYSUCC, and informed consent was waived by the ethics review boards.

All patients were treated with radical IMRT comprising of 5 daily fractions delivered per week for 6–7 weeks. The prescribed doses were 66–72 Gy/28–33 fractions to the planning target volume (PTV) of the primary gross tumor volume (GTVnx), 64–70 Gy/28–33 fractions to PTV of the GTV in involved lymph nodes (GTVnd), 60–63 Gy/28–33 fractions to PTV of the high-risk clinical target volume (CTV1), and 54–56 Gy/28–33 fractions to the PTV of low-risk clinical target volume (CTV2). Institutional guidelines recommended IMRT for stage I NPC, platinum-based concurrent chemoradiotherapy (CCRT) ± induction chemotherapy (IC)/adjuvant chemotherapy (AC) for stages II to IVA NPC. Reasons for deviation from guidelines included recruitment in clinical trials, patient's refusal, age, or organ dysfunction suggesting intolerance to treatment.

Definition of RTT and RTI

Radiation treatment time (RTT) was calculated as the duration from start of RT to completion of planned course. All patients were treated with a fraction daily for 5 days per week, and no planned interruption. RT interruption (RTI) was defined as the radiation treatment time minus the planned radiation time (assuming a Monday start). According to the value of RTI, patients were divided into three groups: (1) exact as planned group (RTI = 0 day); (2) earlier finished group (RTI ≤ -1 day); and (3) more days as expected (RTI ≥ 1 day).

Data sharing

Key raw data were uploaded onto the Research Data Deposit public platform (RDD), with the approval RDD number of RDDA2018000802.

Follow-up

Patients were examined at least every 3 months during the first 2 years, and every 6 months for 3 years thereafter or until death. During visits, clinical examinations and nasopharyngoscopy were routinely performed. Patients with clinical suspicion of recurrence or metastasis were recommended for MRI, whole-body bone scan, abdominal sonography, or PET/CT, followed by confirmatory cytological biopsies if possible. The study's primary endpoint was overall survival (OS), and secondary endpoint was disease-free survival (DFS). We calculated OS as the time from day 1 of treatment to the date of death from any cause. DFS was calculated as the time from day 1 of treatment to the first relapse at any site, death from any cause, or date of the last follow-up visit, whichever occurred first. The median follow-up time was 51.7 months (ranging 1.7–102.5 months).

Statistics analysis

Covariates including host factors (i.e. gender, age, smoking status, drinking status, family history of cancer, hemoglobin [HGB]; high sensitivity C-reactive protein [hs-CRP]; lactate dehydrogenase [LDH]), tumor factors (i.e. pathological types, T and N stage), and treatment factors (i.e. RTT, RTI, prescribed fractions, and treatment modality). Categorical variables were classified according to clinical findings, and continuous variables were transformed into categorical variables based on routine cutoff points or findings reported in previous studies [15–17]. Clinicopathologic characteristics were compared among different groups using χ^2 test or Fisher's Exact Test for frequencies.

Actuarial rates were calculated using the Kaplan–Meier method, and differences were compared using the log-rank test. Recursive partitioning analyses (RPAs) were performed to identify the optimal RTI threshold for the training cohort.

Table 1
Baseline patient characteristics according to RTT.

Characteristic	Median (IQR) RTT, days	No. (%) of patients by RTT in days				Total (N = 7826)*	P value
		≤40 (n = 743, 9.5%)	41–45 (n = 4536, 58.0%)	46–50 (n = 2145, 27.4%)	≥51 (n = 402, 5.1%)		
Gender							0.551
Male	44 (43–46)	533 (71.7)	3299 (72.7)	1586 (73.9)	299 (74.4)	5717 (73.1)	
Female	44 (42–46)	210 (28.3)	1237 (27.3)	559 (26.1)	103 (25.6)	2109 (26.9)	
Histology (WHO)							0.343
Type I–II	44 (43–47)	16 (2.2)	104 (2.3)	57 (2.7)	10 (2.5)	187 (2.4)	
Type III	44 (43–46)	727 (97.8)	4432 (97.7)	2088 (97.3)	392 (97.5)	7639 (97.6)	
Age, year							0.207
≤30	44 (43–47)	68 (9.2)	427 (9.4)	198 (9.2)	40 (10.0)	733 (9.4)	
31–40	44 (43–46)	184 (24.8)	1101 (24.3)	526 (24.5)	80 (19.9)	1891 (24.2)	
41–50	44 (42–46)	253 (34.1)	1608 (35.4)	714 (33.3)	130 (32.3)	2705 (34.6)	
51–60	44 (43–47)	170 (22.9)	964 (21.3)	496 (23.1)	95 (23.6)	1725 (22.0)	
≥61	44 (43–47)	68 (9.2)	436 (9.6)	211 (9.8)	57 (14.2)	772 (9.9)	
Smoking history							0.664
No	44 (43–46)	492 (66.2)	2938 (64.8)	1405 (65.5)	253 (62.9)	5088 (65.0)	
Yes	44 (43–46)	251 (33.8)	1598 (35.2)	740 (34.5)	149 (37.1)	2738 (35.0)	
Drinking history							0.396
No	44 (43–46)	654 (88)	3910 (86.2)	1870 (87.2)	353 (87.8)	6787 (96.7)	
Yes	44 (43–46)	89 (12.0)	626 (13.8)	275 (12.8)	49 (12.2)	1039 (13.3)	
Family of cancer							0.179
No	44 (43–46)	568 (76.4)	3311 (73.0)	1598 (74.5)	293 (72.9)	5770 (73.7)	
Yes	44 (43–46)	175 (23.6)	1225 (27.0)	547 (25.5)	109 (27.1)	2056 (26.3)	
T stage (8th edition)							<0.001
T1	44 (42–46)	161 (21.7)	736 (16.2)	307 (14.3)	44 (10.9)	1248 (15.9)	
T2	44 (42–46)	155 (20.9)	735 (16.2)	276 (12.9)	59 (14.7)	1225 (15.7)	
T3	44 (42–46)	354 (47.6)	2166 (47.8)	1013 (47.2)	175 (43.5)	3708 (47.4)	
T4	45 (44–47)	73 (9.8)	899 (19.8)	549 (25.6)	124 (30.8)	1645 (21.0)	
N stage (8th edition)							0.005
N0	44 (42–46)	140 (18.8)	690 (15.2)	312 (14.5)	43 (10.7)	1185 (15.2)	
N1	44 (43–47)	350 (47.1)	2295 (50.6)	1108 (51.7)	206 (51.2)	3959 (50.6)	
N2	44 (42–46)	176 (23.7)	987 (21.8)	450 (21.0)	96 (23.9)	1709 (21.9)	
N3	44 (43–47)	77 (10.4)	564 (12.4)	275 (12.8)	57 (14.2)	973 (12.4)	
Overall stage (8th edition)							<0.001
I	44 (42–46)	59 (7.9)	227 (5.0)	108 (5.0)	11 (2.7)	405 (5.2)	
II	44 (42–46)	169 (22.7)	803 (17.7)	300 (14.0)	56 (13.9)	1328 (17.0)	
III	44 (42–46)	374 (50.3)	2149 (47.4)	974 (45.4)	169 (42)	3666 (46.8)	
IVa	45 (43–47)	141 (19)	1357 (29.9)	763 (35.6)	166 (41.3)	2427 (31.0)	
HGB, g/L							0.002
<113	45 (43–47)	17(2.3)	152 (3.4)	85 (4.0)	26 (6.5)	284 (3.6)	
113–151	44 (43–46)	485(65.4)	2951 (65.1)	1396 (65.1)	274 (68.2)	5106 (65.2)	
≥151	44 (42–46)	240(32.3)	1432 (31.6)	662 (30.9)	102 (25.4)	2436 (31.1)	
hs-CRP, g/mL							0.137
<1.0	44 (42–46)	269 (49.1)	1509 (46.1)	692 (46.3)	121 (46.5)	2591 (33.1)	
1.0–3.0	44 (43–46)	272 (49.6)	1696 (51.8)	765 (51.2)	131 (50.4)	2864 (36.6)	
≥3.0	45 (43–47)	7 (1.3)	68 (2.1)	38 (2.5)	8 (3.1)	2371 (30.3)	
LDH, U/L							0.105
<245	44 (43–46)	679 (91.8)	4220 (93.1)	1982 (92.4)	354 (88.1)	7235 (92.4)	
≥245	44 (43–47)	61 (8.2)	314 (6.9)	163 (7.6)	48 (11.9)	591 (7.6)	
Prescribed fractions							<0.001
28–30	43 (41–45)	667 (89.8)	2509 (55.3)	688 (32.1)	125 (31.1)	3989 (51.0)	
31–32	45 (43–47)	50 (6.7)	1435 (31.6)	689 (32.1)	115 (28.6)	2289 (29.2)	
33–35	46 (45–49)	26 (3.5)	592 (13.1)	768 (35.8)	162 (40.3)	1548 (19.8)	
Treatment modality							0.001
RT alone	44 (42–46)	91 (12.2)	430 (9.5)	185 (8.6)	34 (8.5)	740 (9.5)	
CCRT	44 (42–46)	277(37.3)	1651 (36.4)	841 (39.2)	132 (32.8)	2901 (37.1)	
IC + CCRT	44 (43–47)	250(33.6)	1850 (40.8)	858 (40)	184 (45.8)	3142 (40.1)	
CCRT + AC	44 (42–46)	48(6.5)	210 (4.6)	83 (3.9)	17 (4.2)	358 (4.6)	
IC + RT	44 (42–46)	77(10.4)	395 (8.7)	178 (8.3)	35 (8.7)	685 (8.8)	

Abbreviation: RTT, radiotherapy treatment time; IQR, inter quartile range; WHO, World Health Organization; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC + CCRT, induction chemotherapy plus concurrent chemoradiotherapy; CCRT + AC, concurrent chemoradiotherapy plus adjuvant chemotherapy; IC + RT, radiotherapy following induction chemotherapy.

* Percentages may not add up to 100 due to rounding.

Covariates with a univariable $P < 0.02$ were included in the multivariable model. The effect of RTI on survival outcomes were estimated using Weibull models, which provides a more reliable and precise assessment than the Cox proportional hazards model [18]. Moreover, we again estimated the effect of RTI in the validation cohort. The criterion for statistical significance was set at an alpha of 0.05, and all P values were based on 2-sided tests. All statistical models were computed with the rms [19] package in R version 3.3.2 (http://www.r-project.org/).

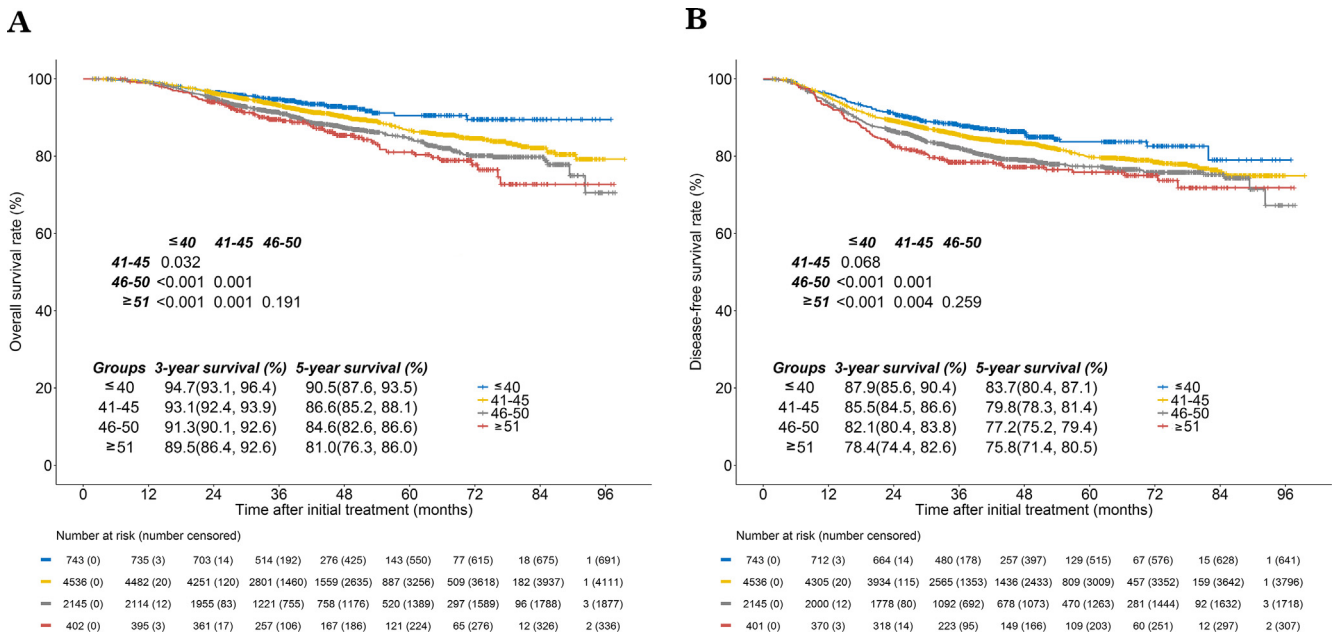

Fig. 1. Kaplan–Meier's plots showed overall survival (A) and disease-free survival (B) divided by the RTT of ≤40 d, 41–45 d, 46–50 d, and ≥51 d, respectively. RTT, radiotherapy treatment time.

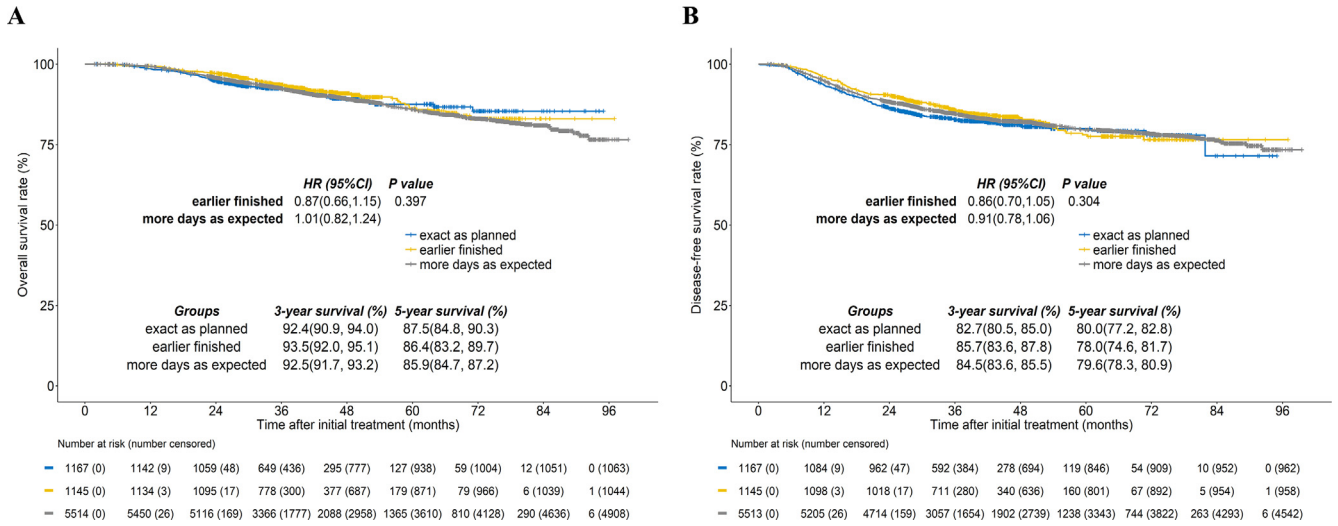

Fig. 2. Comparison of long-term overall survival (A) and disease-free survival (B) probability between the exact as planned group, earlier finished group, and more days as expected group.

Results

Clinical characteristics

Using the linked NPC-specific database, we identified a cohort of 7826 patients diagnosed with NPC between April 2009 and December 2015. Of these 7826 patients, 97.6% had type III disease based on the criteria set by the World Health Organization (WHO), which is non-keratinizing undifferentiated NPC. The median age was 45 years (IQR, 28–53 years), and the male to female ratio was 2.7:1 (men, 5717; women, 2109). The median RTT was 44 d (IQR, 42–46 d) for the entire group, and clinical characteristics were summarized in 5-d intervals (Table 1). Patients with advanced TNM stage (advanced T, N, and/or overall stage) were more likely to have long RTT ($P = 0.001$ for all). Those patients with prescribed fractions of 33–35 more often experienced long RTT ($P < 0.001$). With regard to treatment modality, patients that received IC plus CCRT had longer RTT ($P = 0.001$) in comparison to those not receiving IC plus CCRT. Other features that revealed significant variation included hs-CRP and HGB ($P < 0.001$ for all; Table 1).

Increasing RTT and survival

The 5-year OS rates of RTT ≤ 40 d, 41–45 d, 46–50 d, and ≥51 d were 90.5%, 86.6%, 84.6%, and 81.0%, respectively ($P < 0.05$; Fig. 1A). The difference in DFS rates among RTT ≤ 40 d, 41–45 d, 46–50 d, and ≥51 d were 83.7%, 79.8%, 77.2%, and 75.8%, respectively ($P < 0.05$; Fig. 1B). Overall, for univariate analysis, RTT of 41–45 d (OS: HR 1.38, 95%CI 1.03–1.85; DFS: HR 1.23, 95%CI 1.00–1.51), 46–50 d (OS: HR 1.77, 95%CI 1.31–2.39; DFS: HR 1.48, 95%CI 1.20–1.84), and ≥51 d (OS: HR 2.10, 95%CI 1.45–3.04; DFS: HR 1.65, 95%CI 1.24–2.19) significantly predicted a higher risk of death

Table 2
Baseline patient characteristics according to RTI.

Characteristic	Exact as planned (n = 1167) No. (%)	Earlier finished (n = 1145) No. (%)	More days as expected (n = 5514) No. (%)	P value
Gender				0.288
Male	323 (27.7)	327 (28.6)	1459 (26.5)	
Female	844 (72.3)	818 (71.4)	4055 (73.5)	
Histology (WHO)				0.307
Type I–II	22 (1.9)	24 (2.1)	141 (2.6)	
Type III	1145 (98.1)	1121 (97.9)	5373 (97.4)	
Age, year				0.587
≤30	107 (9.2)	123 (10.7)	503 (9.1)	
31–40	292 (25.0)	276 (24.1)	1323 (24.0)	
41–50	379 (32.5)	384 (33.5)	1942 (35.2)	
51–60	268 (23.0)	251 (21.9)	1206 (21.9)	
≥61	121 (10.4)	111 (9.7)	540 (9.8)	
Smoking history				0.332
No	750 (64.3)	766 (66.9)	3572 (64.8)	
Yes	417 (35.7)	379 (33.1)	1942 (35.2)	
Drinking history				0.792
No	1005 (86.1)	996 (87.0)	4786 (86.8)	
Yes	162 (13.9)	149 (13.0)	728 (13.2)	
Family of cancer				0.016
No	891 (76.3)	864 (75.5)	4015 (72.8)	
Yes	276 (23.7)	281 (24.5)	1499 (27.2)	
T stage (8th edition)				0.002
T1	157 (13.5)	167 (14.6)	924 (16.8)	
T2	190 (16.3)	158 (13.8)	877 (15.9)	
T3	539 (46.2)	568 (49.6)	2601 (47.2)	
T4	281 (24.1)	252 (22.0)	1112 (20.2)	
N stage (8th edition)				0.031
N0	159 (13.6)	186 (16.2)	840 (15.2)	
N1	586 (50.2)	540 (47.2)	2833 (51.4)	
N2	281 (24.1)	276 (24.1)	1152 (20.9)	
N3	141 (12.1)	143 (12.5)	689 (12.5)	
Overall stage (8th edition)				0.038
I	51 (4.4)	58 (5.1)	296 (5.4)	
II	187 (16.0)	169 (14.8)	972 (17.6)	
III	531 (45.5)	562 (49.1)	2573 (46.7)	
IVa	398 (34.1)	356 (31.1)	1673 (30.3)	
HGB, g/L				0.583
<113	37 (3.2)	37 (3.2)	206 (3.7)	
113–151	777 (66.6)	760 (66.4)	3569 (64.8)	
≥151	352 (30.2)	348 (30.4)	1736 (31.5)	
hs-CRP, g/mL				0.907
<1.0	372 (31.9)	381 (33.4)	1838 (33.3)	
1.0–3.0	432 (37.0)	415 (36.3)	2017 (36.6)	
≥3.0	362 (31.0)	346 (30.3)	1657 (30.1)	
LDH, U/L				0.855
<245	1084 (92.9)	1057 (92.6)	5094 (92.4)	
≥245	83 (7.1)	85 (7.4)	418 (7.6)	
Prescribed fractions				<0.001
28–30	343 (29.4)	298 (26.0)	3348 (60.7)	
31–32	534 (45.8)	518 (45.2)	1237 (22.4)	
33–35	290 (24.9)	329 (28.7)	929 (16.8)	
Treatment modality				0.355
RT alone	97 (8.3)	105 (9.2)	538 (9.8)	
CCRT	436 (37.4)	421 (36.8)	2044 (37.1)	
IC + CCRT	487 (41.7)	475 (41.5)	2180 (39.5)	
CCRT + AC	45 (3.9)	42 (3.7)	271 (4.9)	
IC + RT	102 (8.7)	102 (8.9)	481 (8.7)	

Abbreviation: WHO, World Health Organization; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC + CCRT, induction chemotherapy plus concurrent chemoradiotherapy; CCRT + AC, concurrent chemoradiotherapy plus adjuvant chemotherapy; IC + RT, radiotherapy following induction chemotherapy.

compared with RTT of 36–40 d (Supplementary Table S1). Consistent with univariate analysis, RTT of 41–45 d (HR, 1.36; 95%CI 1.01–1.82), 46–50 d (HR, 1.76; 95%CI 1.16–2.68), and ≥51 d (HR, 1.84; 95%CI 1.11–3.07) independently elevated the risk of mortality compared to ≤40 d in multivariate analysis (Supplementary Table S2), however, failed to retain statistical significance in predicting DFS (P > 0.05 for all).

RPAs were used to identify the optimal thresholds of RTT to predict the largest differences in survival, since multivariate Weibull analysis revealed that RTT was an independent risk factor for survival. The optimal thresholds of RTT for OS was 42.5 d based on PRAs. Adjusted risk for two groups based on optimal threshold of 42 d was provided for the entire group (RTT of ≥42 d vs <42 d), and RTT of ≥42 d still presented significant detrimental effects

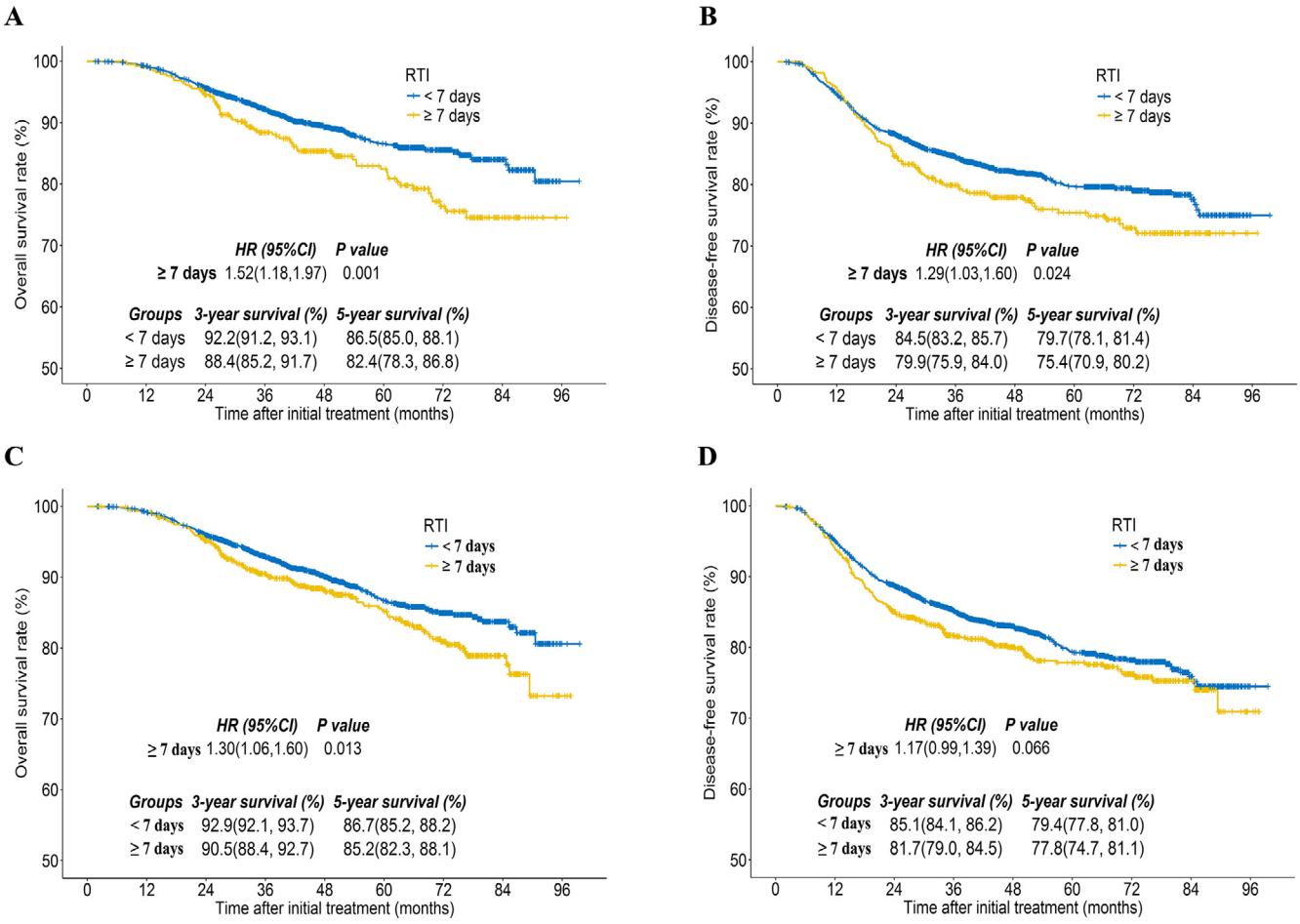

Fig. 3. Kaplan–Meier's curves of overall survival and disease-free survival in the training cohort (top); Kaplan–Meier's curves of overall survival and disease-free survival in the validation cohort (bottom). The four top and bottom curves are stratified by RTI (<7 d vs ≥7 d). RTI, radiotherapy interruption.

on OS (5-y, 84.8% vs 90.4%, $P < 0.001$; Supplementary Fig. S1A) and DFS (5-y, 78.4% vs 81.8%, $P < 0.001$; Supplementary Fig. S1B) than patients with RTT of <42 d.

Survival comparison of patients stratified by RTI

For the entire group, patients were divided into three groups according to whether the patient completed the radiotherapy plan on time. Although the exact as planned group (87.5%) had a higher 5-year OS compared with earlier finished group (86.4%) and more days as expected group (85.9%), no significant differences in OS were observed among each group ($P = 0.397$; Fig. 2A). Likewise, the DFS curves for these above three groups nearly overlapped, with no significant differences as well ($P = 0.304$; Fig. 2B). Further analyses revealed that no significant differences in host factors and treatment factors were identified among the above three groups, apart from TNM stage, family of cancer, and prescribed fractions ($P < 0.05$ for all; Table 2). In addition, the exact as planned group had a significantly higher ratio of advanced T stage ($P = 0.002$), N stage ($P = 0.031$), and overall stage ($P = 0.038$) in comparison with other two groups (Table 2).

Second analysis on the prognostic value of RTI in the training and validation cohort

Using computer-generated random numbers, two well-balanced groups ($P > 0.050$ for all) were created to research the prognostic value of RTI. Detailed characteristics of the training/validation cohorts are described in Supplementary Table S3. The optimal cutoff point for RTI with respect to OS in the training set ($n = 3913$) was 6.5 d based on RPAs. Therefore, we selected a uniform cutoff point of 7 d (<7 vs. ≥7 d) to classify the training cohort and validation cohort into high and low RTI groups for survival analysis. In the training cohort, RTI of ≥7 d showed significant detrimental effects on OS (5-y, 82.4% vs 86.5%; $P = 0.001$) (Fig. 3A) and DFS (5-y, 75.4% vs 79.7%; $P = 0.024$) (Fig. 3B) than those patients with RTI of <7 d. Multivariate analysis was performed to adjust for various prognostic factors. Consistent with results of the univariate analysis, RTI of ≥7 d was found to be an independent unfavorable prognostic factor for OS (HR, 1.49; 95% CI, 1.14–1.95; $P = 0.003$) and DFS (HR, 1.29; 95% CI, 1.03–1.62; $P = 0.028$) (Table 3).

Similarly, patients with RTI ≥ 7 d had significantly lower OS rate in comparison with RTI < 7 d (HR, 1.30; 95% CI, 1.06–1.60; $P = 0.013$; Fig. 3C) in the validation cohort. Multivariate analysis also showed that RTI was an independent prognostic factor and RTI of ≥7 d was associated with inferior OS (HR, 1.37; 95% CI, 1.07–1.65; $P = 0.031$; Table 4). In contrast, although RTI of ≥7 d tended to be inferior for DFS compared with RTI < 7 d (79.4% vs. 77.8%, respectively), the difference did not reach statistical significance ($P = 0.066$) in the validation cohort (Fig. 3D; Table 4).

Interaction effects of RTI with other covariates

Interaction effects of RTI were assessed for T stage (categorized as T1-2 or T3-4), overall stage (classed as stage I–II or III–IVa),

Table 3
Multivariable analysis of the Weibull parametric proportional hazard model adjusted for covariates to estimate the risk of overall and disease-free survival in the training cohort.

Characteristic	Overall survival		Disease-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	Reference		Reference	
Female	1.13(0.85,1.48)	0.405	1.15 (0.97,1.37)	0.109
Histology (WHO)				
Type I–II	Reference		Reference	
Type III	0.60(0.39,0.92)	0.02	0.60(0.42,0.86)	0.005
Age, year				
≤30	Reference		Reference	
31–40	0.97(0.65,1.45)	0.88	1.34(0.98,1.82)	0.063
41–50	1.15(0.79,1.68)	0.47	1.29(0.95,1.74)	0.098
51–60	1.56(1.06,2.30)	0.024	1.45(1.07,1.99)	0.018
≥61	2.18(1.43,3.31)	0	1.80(1.28,2.55)	0.001
Smoking history				
No	Reference		Reference	
Yes	1.04(0.84,1.30)	0.705	1.05(0.90,1.23)	0.519
T stage (8th edition)				
T1	Reference		Reference	
T2	1.24(0.80,1.92)	0.332	1.53(1.09,2.14)	0.014
T3	1.62(1.11,2.38)	0.013	1.82(1.35,2.45)	0
T4	2.55(1.70,3.84)	0	2.55(1.85,3.52)	0
N stage (8th edition)				
N0	Reference		Reference	
N1	1.52(1.03,2.25)	0.033	1.53(1.14,2.06)	0.005
N2	2.37(1.56,3.59)	0	2.20(1.60,3.02)	0
N3	3.36(2.20,5.14)	0	2.89(2.08,4.03)	0
HGB, g/L				
<113	Reference		Reference	
113–151	0.60(0.38,0.96)	0.033	0.69(0.48,0.99)	0.045
≥151	0.54(0.35,0.83)	0.005	0.69(0.49,0.97)	0.033
hs-CRP, g/mL				
<1.0	Reference		Reference	
1.0–3.0	1.48(1.13,1.92)	0.004	1.21(1.00,1.48)	0.052
≥3.0	1.39(1.07,1.81)	0.014	1.11(0.92,1.35)	0.281
LDH, U/L				
<245	Reference		Reference	
≥245	1.75(1.32,2.33)	0	1.54(1.22,1.95)	0
Prescribed fractions				
28–30	Reference		Reference	
31–32	1.35(1.04,1.73)	0.022	1.26(1.03,1.54)	0.023
33–35	1.14(0.89,1.46)	0.293	1.18(0.98,1.42)	0.075
Treatment modality				
RT alone	Reference		Reference	
CCRT	0.67(0.45,0.99)	0.046	0.91(0.65,1.27)	0.582
IC + CCRT	0.65(0.43,0.97)	0.037	0.85(0.60,1.20)	0.351
CCRT + AC	0.85(0.48,1.48)	0.554	0.93(0.58,1.47)	0.749
IC + RT	0.72(0.45,1.15)	0.167	0.91(0.61,1.34)	0.621
RTT, days				
≤7	Reference		Reference	
≥7	1.49(1.14,1.95)	0.003	1.29(1.03,1.62)	0.028

Abbreviation: HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC + CCRT, induction chemotherapy plus concurrent chemoradiotherapy; CCRT + AC, concurrent chemoradiotherapy plus adjuvant chemotherapy; IC + RT, radiotherapy following induction chemotherapy; RTT, radiotherapy treatment time.

treatment modality one (categorized as "with CCRT" or "without CCRT"), and treatment modality two (classed as "with IC" or "without IC"). Risk was adjusted in two groups based on best threshold of 7 d. Compared with RTI of <7 d, RTI of ≥7 d presented significant inferior prognosis in both early and advanced T stage ($P < 0.05$ for all; Fig. 4a1-2). Although an association was observed for longer RTI with inferior OS in patients with stage III–IVa ($P = 0.024$; Fig. 4b2), no association was found between RTI and OS with stage I–II ($P = 0.089$; Fig. 4b1). Further analysis revealed that only 6.2% (172/1733) of patients with stage I–II experienced periods of RTI under 7 d during radical RT. Regarding chemotherapy, RTI of ≥7 d was significantly associated with inferior survival for patients treated with or without CCRT ($P < 0.05$ for all; Fig. 4c1-2). Although an association was observed for RTI of ≥7 d with inferior OS in patients treated without IC ($P = 0.009$; Fig. 4d2), no association was found for patients treated with IC ($P = 0.130$; Fig. 4d1).

Discussion

Currently, this is the largest population-based study to evaluate the effect of RTI on survival in NPC patients in an endemic area. Based on nearly 8000 patients, significant relationships between RTI and NPC survival were established. Our analyses indicated the detrimental effects of prolonging RTT on NPC prognosis, and further analysis revealed that increasing RTI of ≥7 d was associated with increased mortality whether in a training or validation cohort. Though unable to determine a causal relationship between prognosis and RTI, it is conceivable that reduced RTT may decrease mortality for NPC in the IMRT era.

Although several studies have indicated that prolonged RTT would result in poorer survival in NPC, there are concepts mainly derived from the 2DRT era [4–6]. An explanation for this observation is the result of accelerated repopulation of tumor cells during

Table 4
Multivariable analysis of Weibull parametric proportional hazard model adjusted for covariates to estimate the risk of overall and disease-free survival in the validation cohort.

Characteristic	Overall survival		Disease-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	Reference		Reference	
Female	1.38(1.03,1.85)	0.032	1.22(0.99,1.50)	0.069
Histology (WHO)				
Type I–II	Reference		Reference	
Type III	0.60(0.36,1.00)	0.048	0.66(0.43,1.01)	0.058
Age, year				
≤30	Reference		Reference	
31–40	1.76(1.07,2.89)	0.025	1.33(0.94,1.87)	0.104
41–50	1.88(1.16,3.04)	0.01	1.59(1.15,2.21)	0.005
51–60	2.34(1.44,3.81)	0.001	1.58(1.13,2.22)	0.008
≥61	3.61(2.17,6.01)	0	2.05(1.42,2.97)	0
Smoking history				
No	Reference		Reference	
Yes	1.10(0.87,1.39)	0.442	1.33(1.11,1.59)	0.002
T stage (8th edition)				
T1	Reference		Reference	
T2	2.21(1.35,3.64)	0.002	2.37(1.65,3.40)	0
T3	2.28(1.46,3.57)	0	2.20(1.59,3.06)	0
T4	4.03(2.52,6.44)	0	3.49(2.46,4.95)	0
N stage (8th edition)				
N0	Reference		Reference	
N1	1.64(1.06,2.53)	0.025	1.88(1.34,2.63)	0
N2	2.80(1.79,4.39)	0	3.09(2.17,4.39)	0
N3	3.99(2.47,6.42)	0	4.45(3.07,6.44)	0
HGB, g/L				
<113	Reference		Reference	
113–151	0.53(0.32,0.87)	0.013	0.75(0.52,1.09)	0.122
≥151	0.56(0.35,0.88)	0.013	0.70(0.49,1.00)	
hs-CRP, g/mL				
<1.0	Reference		Reference	
1.0–3.0	1.25(0.96,1.61)	0.093	1.16(0.95,1.41)	0.143
≥3.0	0.87(0.67,1.14)	0.318	0.92(0.76,1.12)	0.409
LDH, U/L				
<245	Reference		Reference	
≥245	1.90(1.43,2.52)	0	1.59(1.26,2.00)	0
Prescribed fractions				
28–30	Reference		Reference	
31–32	1.16(0.88,1.52)	0.291	1.17(0.96,1.44)	0.122
33–35	1.15(0.90,1.48)	0.269	1.05(0.87,1.27)	0.58
Treatment modality				
RT alone	Reference		Reference	
CCRT	1.14(0.72,1.81)	0.568	0.96(0.67,1.38)	0.819
IC + CCRT	0.79(0.49,1.26)	0.321	0.83(0.58,1.21)	0.334
CCRT + AC	0.95(0.48,1.86)	0.873	0.86(0.52,1.43)	0.561
IC + RT	1.11(0.65,1.88)	0.702	0.83(0.54,1.28)	0.393
RTT, days				
≤7	Reference		Reference	
≥7	1.37(1.07,1.65)	0.031	1.17(0.89,1.41)	0.135

Abbreviation: HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC + CCRT, induction chemotherapy plus concurrent chemoradiotherapy; CCRT + AC, concurrent chemoradiotherapy plus adjuvant chemotherapy; IC + RT, radiotherapy following induction chemotherapy; RTT, radiotherapy treatment time.

radiation interruptions [20]. Our results also confirmed that prolonged RTT affects survival based on a larger population with multiple groups in the IMRT era. Further analysis revealed that prolonged RTT of ≥42 d was associated with inferior prognosis. Considering the fractionation scheme was not uniform in the current study, the cutoff of 42 d would mean a different delay depending on the initial fractionation schedule. This suggests that the duration of RTT could not accurately assess the impact of RTI on the prognosis of patients. Therefore, we directly analyzed the effect of RTI on survival according to whether the patient completed the RT plan on time. Unexpectedly, although patients who completed RT as planned presented higher OS and DFS rates than those in the earlier finished and more days as expected groups, this trend did not reach statistical significance. Considering that advanced TNM stage was associated with inferior survival [21,22] we hypothesize our finding of no statistical association is largely due to higher ratio of advanced TNM stage in the group of completed RT exact as planned.

Currently, the effect of RTI during radical IMRT on the prognosis of NPC remains controversial [8,12]. Stoker and colleagues [12] recently estimated the effects of RTI on survival of NPC patients treated with radical IMRT. They observed no associated trend toward poorer prognosis for lengthier RTI. However, their study had a small sample size (n = 142), limiting the ability to identify an effect. Another study included 515 patients with limited clinical characteristics (e.g. age, sex, histology, TNM stage, and chemotherapy) observed that an RTI greater than four days during IMRT was associated with inferior OS and DFS for NPC with short follow-up time [8]. However, RTIs were not analyzed as a continuous variable nor multigroup in their study. For this reason, their findings that greater than four days of RTI results in poor prognosis should be interpreted with caution, even though the two groups had statisti-

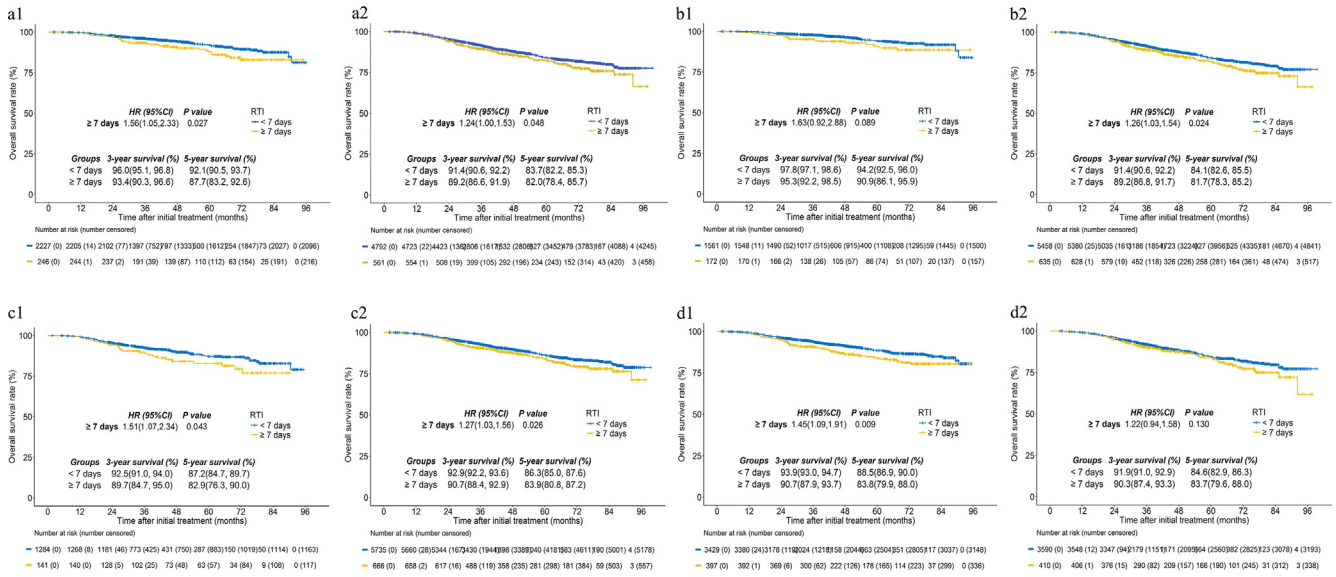

Fig. 4. Kaplan–Meier's plots showed overall survival divided by the optimal threshold of RTI (<7 d vs ≥7 d) in patients with T1–2 stage (a1), T3–4 stage (a2), stage I–II (b1), stage III–IVa (b2), treated without CCRT (c1), treated with CCRT (c2), treated without IC (d1), and treated with IC (d2), respectively. RTI, radiotherapy interruption; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

cally associated differences in their study. To ensure the reliability of the results, we included nearly 8000 patients and divided them into training and validation groups using computer-generated random numbers. Our results confirmed that RTI of ≥7 d was significantly associated with inferior survival in both training and validation cohorts. Our findings suggest that additional effort needs to be made to limit RTI under 7 d to avoid risk of associated adverse health effects.

In subgroup analyses, prolonged RTI was confirmed as an independent adverse prognostic factor for patient survival whether during T1-2 or T3-4 stage. Although an association was observed for longer RTI with inferior OS in patients with stages III–IVa, no association was found between RTI and OS with stages I–II. Our findings do not reflect that elevated RTI does not affect the survival of NPC patients with stages I–II. A potential reasoning is that only 9.9% (172/1733) of patients with stage I–II experienced periods of RTT more than 7 d from our data, which could hinder the results from reaching statistical association. Several prospective randomized trials [23–25] and meta-analysis [26,27] have illustrated that the addition of chemotherapy to radiation is better than RT alone for managing NPC stages II–IVB. Regarding the chemotherapy effect, some authors suggested that when IMRT was introduced for management of NPC, the effect of increasing RTI on treatment outcomes were negated [10,11]. Our results indicated increasing RTI ≥ 7 d had significant detrimental effects on survival irrespective of whether they received CRT or not. Although there were no significant survival difference between RTI of <7 d in comparison to ≥7 d during the first 5 years after initial treatment for patients treated with IC, the survival of RTI ≥ 7 d curve drops sharply compared to the survival of RTI < 7 d curve after 5 years of initial treatment. This potentially indicates that there was a delayed effect of RTI on survival of NPC patients treated with IC. However, the latent mechanism by which IC leads to a delayed effect of RTI on survival needs to be investigated further.

A main strength of the present study is the use of a large-scale data derived from real-world medical records, which reflects the actual medical treatment process and influence of RTI under real conditions. Nevertheless, there are some limitations that must be noted. First, we calculated RTT from the start of RT to completion of the planned course, though failed to collect information on the detailed characteristic of whether RTI was continuous interruption or discontinuous interruption as the effect of RTI might be different as a result. Second, although our research incorporates internal validation which ensured the generalizability of the results to other patient populations to an extent, scaled studies that incorporate external validation are still necessary to validate our findings. Finally, since the intelligence platform failed to collect the date on acute and late toxicities, treatment-related toxicities were lacking.

In summary, our large cohort study focusing on patients with NPC reveals an association between extended RTI and poor survival irrespective of TNM stage and treatment modality in the IMRT era. Further analysis revealed that the optimal threshold of RTI that adversely effects NPC prognosis in the IMRT era was 7 days. Given the detrimental effect of RTI on survival outcomes, additional effort needs to be made to limit RTI during RT under 7 d in clinical practice.

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Conflict of interest statement

None.

Data statement

Key raw data were uploaded onto the Research Data Deposit public platform (RDD), with the approval RDD number of RDDA2018000802.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.018.

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