Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Quantification of Plasma EBV DNA

Samples of peripheral blood (5 ml) were collected from all patients and were centrifuged at 1600 × *g* for plasma isolation. 500–1000 μl of each plasma sample were used for DNA extraction following the instruction of the QIAamp Blood Kit (Qiagen, Hilden, Germany). The polymerase chain reaction (PCR) assay targeting the BamHI-W region was performed to quantify the EBV DNA level. The system consisted of the amplification primers W-44F (5′- AGTCTCTGCCTCCAGGCA-3′) and W-119R (5′-ACAGAGGGCCTGTCCACC G-3′) and the dual-labeled fluorescent probe W-67T (5′- [FAM] CACTGTCTGTAAAGTCCAGCCTCC [TAMRA]-3′).

eAppendix 2. Description of the Guidelines for IMRT in This Trial

Patients were immobilized in the supine position and fitted with a thermoplastic mask, which covered the head, neck, and shoulder. Both non-enhanced CT (for dose calculation) and contrast- enhanced CT (for target delineation) images were obtained from the vertex to 2 cm below the sternoclavicular joint, with 3-mm slices.

Delineation of target volumes was performed according to the International Commission on Radiation Units and Measurements reports 50 and 62. The gross tumor volume (GTV) included the primary tumor volume, the enlarged retropharyngeal lymph nodes (GTVnx), and the involved cervical lymph nodes (GTVnd). The high-risk clinical target volume (CTV1) was defined as the GTVnx plus a 5–10-mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. The low dose clinical target volume (CTV2) was defined as the CTV1 plus a 5–10-mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the low-risk sites of microscopic extension, including the foramen lacerum, sphenoid sinus, clivus, oval foramen, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, the cervical level where the involved lymph nodes were located, and the elective neck area from level II to V (according to the patient's treatment group). Level Ib was electively irradiated if any of the following existed: (1) Level Ib lymph nodes (LNs) were involved, (2) level IIa LNs with a diameter ≥ 3 cm or extracapsular extension, (3) extensive nodal disease existing on the ipsilateral neck, and (4) any of the oral cavity, soft or hard palate, or ipsilateral nasal cavity was grossly involved. A planning target volume (PTV) was created by adding a three-dimensional margin of 3–5 mm to the delineated target volume to compensate for the uncertainties in treatment set-up and internal organ motion. A 3-mm margin was added to the critical organs (e.g., brainstem and spinal cord) to form the planning organ at risk volume (PRV).

The recommended doses were 68–70 Gy, 66–70 Gy, 60–62 Gy, and 54–56 Gy, in 30–33 fractions (once per day, five fractions every week), for the PTVs derived from GTVnx, GTVnd, CTV1, and CTV2, respectively. However, the radiation doses could be adjusted moderately according to the tumor volume. All plans were generated by a team of dosimetrists using a whole field (including neck radiation) simultaneous integrated boost technique. In general, target volume coverage could be compromised if critical normal tissues (e.g., brainstem and spinal cord) were adjacent to the high-dose target volumes, to keep these critical normal tissues within the dose constraints. When other normal tissues of lower priority were adjacent to the high-dose

target volumes, the dose to these tissues was kept as low as possible under the premise of not compromising the target coverage. The trade-off case was discussed and decided upon by the research team at each participating center.

Quality assurance of delineation and dose coverage was performed by the research team at the Sun Yat-sen University Cancer Center. The participating centers were required to submit dose data of the gross tumor, the clinical target, and the surrounding critical structures to the principal center, before the initiation of radiotherapy treatment. The Principal Investigator/Radiation Oncologist, Ling-Long Tang, MD, performed RT Quality Assurance Reviews of all participating centers. In addition, quality assurance for radiotherapy procedures were performed by the research team at each participating center. If patients received induction chemotherapy, radiotherapy was recommended to start within 21–28 days of the first day of the last cycle of induction chemotherapy. In addition, GTV was delineated according to the pre-induction chemotherapy tumor extension, and dose modifications were not allowed. The normal tissue dose constraints are listed as follows.

Structure	Dose constraints
Spinal cord	Dmax* ≤ 45 Gy
Spinal cord_PRV	D1†≤ 50 Gy
Brain stem	Dmax ≤ 54 Gy
Brain stem_PRV	D1 ≤ 60 Gy
Optic nerves	Dmax ≤ 54 Gy
Optic nerves_PRV	D1 ≤ 60 Gy
Optic chiasm	Dmax ≤ 54 Gy
Optic chiasm_PRV	D1 ≤ 60 Gy
Temporal lobe	Dmax ≤ 60 Gy
Temporal lobe_PRV	D1 ≤ 65 Gy
Lens	Dmean‡ < 8 Gy
Pituitary	Dmax < 60 Gy
Thyroid	Dmean < 35 Gy
Eyes	Dmean < 35 Gy
Mandible	Dmax < 70 Gy
Temporomandibular Joint	Dmax < 70 Gy
Parotid	Dmean < 26 Gy
Parotid	V30§ < 50%
Cochlea	Dmean < 50 Gy

Larynx	Dmean < 45 Gy
Trachea	Dmean <45 Gy
Esophagus	V35 < 50%

PRV = planning organ at risk volume.

* Maximum point dose to the target volume.

† Dose received by 1% of the target volume.

‡ Mean dose to the target volume.

§ At least 50% of the gland will receive < 30 Gy (should be achieved in at least one gland).

eAppendix 3. Definitions of the End Points

Failure-free survival (FFS) was defined as the interval between randomization and distant failure, locoregional failure, or death from any cause, whichever happened first. Overall survival was defined as the time from random assignment to death from any cause. Distant metastasis-free survival was defined as the interval from randomization to the first distant metastasis or death from any cause. Locoregional relapse-free survival was defined as the interval from randomization to the first local or regional recurrence, or death from any cause. Patients with a distant recurrence as a first event were censored for locoregional recurrence and vice versa. If both distant and locoregional recurrences occurred at the same time, patients were considered as having an event for both distant metastasis-free survival and locoregional relapse-free survival. Patients who were lost to follow-up, or are still alive without distant metastasis or locoregional recurrence were censored at the date of last follow-up.

eTable 1. Recruitment by Center

Center	Principle investigator	Patients
Sun Yat-sen University Cancer Centre	Ling-Long Tang	251
First People's Hospital of Foshan	Ning Zhang	60
The Wuzhou Red Cross Hospital	Bin Deng	20
The fifth Affiliated Hospital of Sun Yat-sen University	Zhi Bin Chen	8
Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	Kun Yu Yang	2

eTable 2. Salvage Treatments After Disease Failure

Treatment type	IMRT alone group (N =172)	CCRT group (N = 169)
	number of patients with event	
Treatment after locoregional recurrence	N = 13	N = 11
Surgery	5	5
Radiotherapy	0	1
Chemotherapy	1	0
Immunotherapy	0	0
Targeted therapy	0	0
Multiple	5	5
Supportive care	1	0
Unknown	1	0
Treatment after distant metastasis	N = 8	N = 4
Surgery	1	1
Radiotherapy	0	0
Chemotherapy	1	1
Immunotherapy	0	0
Targeted therapy	0	0
Multiple	5	2
Supportive care	1	0
Unknown	0	0

CCRT = concurrent chemoradiotherapy

eTable 3. Distribution of Disease Failure

Event	IMRT alone group (N =172)	CCRT group (N = 169)
	number of patients with event (percent)	
Disease failure	20 (11.6)	15 (8.9)
Distant	8 (4.7)	4 (2.4)
Lung	2 (1.2)	0
Bone	2 (1.2)	1 (0.6)
Liver	1 (0.6)	1 (0.6)
Other	0	0
Multiple	3 (1.7)	2 (1.2)
Locoregional	13 (7.6)	11 (6.5)
Local alone	10 (5.8)	7 (4.1)
Regional alone	2 (1.2)	3(1.8)
Local + regional	1 (0.6)	1 (0.6)
Distant + Locoregional	2 (1.2)	0
Distant + local	1 (0.6)	0
Distant + regional	0	0
Distant + local + regional	1 (0.6)	0
Death	6 (3.5)	2 (1.2)
Cancer-specific	5 (2.9)	2 (1.2)
Non-cancer-specific	1 (0.6)	0
Nasopharyngeal necrosis	--	--
Gastrorrhagia	--	--
Cerebrovascular diseases	--	--
Respiratory disease	--	--
Accident	--	--
Unknown	1 (0.6)	--

* Percentages may not total 100 because of rounding.

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eTable 4. Radiotherapy for 2 Groups and Compliance to CCRT

Variable	IMRT alone group	CCRT group
No. patients randomized	172	169
Patients starting RT, no. (%)	172(100%)	169(100%)
Patients completing RT, no. (%)	171(99.4%)	169(100%)
Median (interquartiles) dose of RT (Gy)	70(70-70)	70 (70-70)
Median (interquartiles) dose per fraction (Gy)	2.12(2.12-2.12)	2.12 (2.12-2.12)
Median (interquartiles) duration of RT (days)	45(44-46)	45 (44-47)
Patients completing at least two cycles CC, no. (%)		164(97.0%)
Patients completing three cycles CC, no. (%)		102 (60.4%)
Patients received concurrent dosage more than 200 mg/m²		150 (88.8%)

CCRT = concurrent chemoradiotherapy

eTable 5. Multivariable Analyses of Prognostic Factors by Outcome for Patients in Full Set

	Events, n/N (%) or median (IQR)	Hazard ratio (95% CI)	p value
Failure-free survival			
Sex			
Male	24/239 (10.0%)	1 (ref)	
Female	11/102 (10.8%)	1.03 (0.50–2.14)	.93
Age (per year increase)	48 (41-56)	1.00 (0.97–1.03)	.93
T category			
T1	5/69 (7.2%)	1 (ref)	
T2	20/185 (10.8%)	1.45 (0.51–4.12)	.48
T3	10/87 (11.5%)	1.32 (0.31–5.68)	.71
N category			
N0	16/136 (11.8%)	1 (ref)	
N1	19/205 (9.3%)	0.84(0.32–2.24)	.73
Cheomotherapy group			
CCRT group	15/169 (8.9%)	1 (ref)	
IMRT alone group	20/172 (11.6%)	1.36 (0.70-2.67)	.37
Overall survival			
Sex			
Male	6/239 (2.5%)	1 (ref)	
Female	2/102 (2.0%)	0.54 (0.11–2.76)	.46
Age (per year increase)	48 (41-56)	1.06 (0.98–1.14)	.13
T category			
T1	1/69 (1.4%)	1 (ref)	
T2	5/185 (2.7%)	2.40 (0.27–21.52)	.43
T3	2/87 (2.3%)	70994.79 (0.00–1.04E+140)	.94
N category			
N0	2/136 (1.5%)	1 (ref)	
N1	6/205 (2.9%)	60828.98 (0.00–8.83E+139)	.95
Cheomotherapy group			
CCRT group	2/169 (1.2%)	1 (ref)	
IMRT alone group	6/172 (3.5%)	2.92(0.58–14.63)	.19
Distant metastasis-free survival			

Sex			
Male	7/239 (2.9%)	1 (ref)	
Female	5/102 (4.9%)	1.32 (0.40–4.31)	.65
Age (per year increase)	48 (41-56)	1.05 (0.99–1.11)	.14
T category			
T1	2/69 (2.9%)	1 (ref)	
T2	7/185 (3.8%)	1.42 (0.28–7.21)	.67
T3	3/87 (3.4%)	41303.35(0.00–5.84E+107)	.93
N category			
N0	3/136 (2.2%)	1 (ref)	
N1	9/205 (4.4%)	44384.90 (0.00–6.23E+107)	.93
Cheomotherapy group			
CCRT group	4/169 (2.4%)	1 (ref)	
IMRT alone group	8/172 (4.7%)	2.00 (0.60–6.67)	.26
Locoregional relapse-free survival			
Sex			
Male	18/239 (7.5%)	1 (ref)	
Female	7/102 (6.9%)	0.95 (0.39–2.30)	.90
Age (per year increase)	48 (41-56)	0.98 (0.94–1.02)	.32
T category			
T1	3/69 (4.3%)	1 (ref)	
T2	14/185 (7.6%)	1.51 (0.39–5.81)	.55
T3	8/87 (9.2%)	0.99(0.18–5.54)	.99
N category			
N0	14/136 (10.3%)	1 (ref)	
N1	11/205 (5.4%)	0.44 (0.15–1.31)	.14
Cheomotherapy group			
CCRT group	11/169 (6.5%)	1 (ref)	
IMRT alone group	14/172 (8.1%)	1.29 (0.58–2.85)	.53

All hazard ratios are adjusted for other covariates.
IQR: Inter-Quartile Range; CCRT = concurrent chemoradiotherapy

eTable 6. Baseline Characteristics Among Patients Who Were Analyzed for EORTC QLQ-C30 Questionnaires

	IMRT alone group (n = 108)	CCRT group (n = 109)	P value
Sex			.29*
Male	68 (63.0%)	76 (69.7%)	
Female	40 (37.0%)	33 (30.3%)	
Median age (years)	48.5 (22–67)	49 (23–66)	.67§
Karnofsky score			>0.99†
70–80	0	1 (0.9%)	
90–100	108 (100.0%)	108 (99.1%)	
Tumour category‡			.59*
T1	19 (17.6%)	17 (15.6%)	
T2	51 (47.2%)	59 (54.1%)	
T3	38 (35.2%)	33 (30.3%)	
Nodal category‡			.54*
N0	50 (46.3%)	46 (42.2%)	
N1	58 (53.7%)	63 (57.8%)	
Stage‡			.53*
II	70 (64.8%)	75 (68.8%)	
III	38 (35.2%)	34 (31.2%)	

*P-values were calculated using a χ^2 test.
§P-values were calculated using T-test.
†P-values were calculated using Fisher's exact test.
‡ According to the American Joint Committee on Cancer staging system, 7th edition.
CCRT = concurrent chemoradiotherapy

eTable 7. Pretreatment Quality-of-Life Scores of Patients

	IMRT alone group mean (SD)	CCRT group mean (SD)	Difference (95% CI)	P-value*
EORTC QLQ-C30	N = 108	N = 109		
General QoL (the higher the better)				
Global health status	80.09 (13.76)	79.66 (12.18)	0.43 (–3.04 to 3.91)	.76
Physical functioning	95.49(7.05)	94.43(7.62)	1.06 (–0.90 to 3.02)	.28
Role functioning	92.13 (13.18)	93.73 (12.99)	–1.60 (–5.10 to 1.90)	.23
Emotional functioning	86.57 (12.68)	87.92(13.44)	–1.34 (–4.84 to 2.15)	.32
Cognitive functioning	93.06(10.22)	91.74(13.54)	1.31 (–1.90to 4.52)	.94
Social functioning	85.03 (20.63)	83.33 (20.66)	1.70 (–3.83 to 7.22)	.45
Symptom burden (the lower the better)				
Fatigue	11.83 (12.37)	12.03(12.93)	-0.20 (–3.58to 3.19)	.98
Nausea and vomiting	3.24 (7.37)	2.60 (6.07)	0.64 (–1.17to 2.45)	.65
Pain	4.01 (8.79)	3.98 (8.15)	0.04 (–2.23 to 2.30)	.83
Dyspnea	5.25(12.20)	4.89 (11.85)	0.35 (–2.86 to 3.57)	.83
Insomnia	9.88 (16.59)	8.87 (15.48)	1.01 (–3.29 to 5.30)	.70
Appetite loss	9.57 (15.15)	10.70 (15.63)	–1.14 (–5.26 to 2.98)	.59
Constipation	4.63(11.58)	5.50 (12.43)	-0.87 (–4.09 to 2.34)	.59
Diarrhea	2.78 (9.26)	2.14 (8.21)	0.64 (–1.70 to 2.98)	.59
Financial difficulties	21.60 (28.57)	21.10(27.47)	0.50 (–7.00 to 8.00)	.97

*P-values were calculated using Mann–Whitney U tests.
CCRT = concurrent chemoradiotherapy

eTable 8. Mean Differences in Quality-of-Life Scores Between Treatment Groups

	IMRT alone group	CCRT group	Mean difference 95% CI	P-value
EORTC QLQ-C30				
General quality of life (the higher the better)				
Global health status	71.1(70.0 to 72.2)	58.9(57.8 to 60.0)	12.2(10.6 to 13.8)	<.001
Physical functioning	92.4(91.6 to 93.1)	84.3(83.5 to 85.1)	8.1(7.0 to 9.2)	<.001
Role functioning	84.2(83.0 to 85.5)	79.2(78.0 to 80.4)	5.0 (3.3 to 6.8)	<.001
Emotional functioning	86.4(85.4 to 87.4)	80.7(79.7 to 81.7)	5.7 (4.3 to 7.1)	<.001
Cognitive functioning	91.6(90.6 to 92.5)	84.5(83.6 to 85.5)	7.0 (5.7 to 8.4)	<.001
Social functioning	83.1(81.6 to 84.6)	72.3(70.9 to 73.8)	10.8 (8.7 to 12.8)	<.001
Symptom burden (the lower the better)				
Fatigue	17.3(16.1 to 18.5)	29.1(27.9 to 30.2)	-11.8(-13.4 to -10.2)	<.001
Nausea and vomiting	9.0(7.8 to 10.2)	21.8(20.6 to 23.0)	-12.8(-14.5 to -11.1)	<.001
Pain	11.2(10.1 to 12.2)	21.3(20.3 to 22.4)	-10.2(-11.7 to -8.7)	<.001
Dyspnoea	6.5(5.4 to 7.5)	13.3(12.3 to 14.3)	-6.8(-8.3 to -5.4)	<.001
Insomnia	17.4(15.9 to 18.9)	27.7(26.2 to 29.2)	-10.4(-12.5 to -8.2)	<.001
Appetite loss	18.7(17.2 to 20.2)	33.9(32.4 to 35.5)	-15.2(-17.4 to -13.1)	<.001
Constipation	7.0(5.6 to 8.4)	24.8(23.5 to 26.2)	-17.8(-19.8 to -15.9)	<.001
Diarrhoea	4.0(3.2 to 4.9)	4.8(4.0 to 5.7)	-0.8(-2.0 to 0.4)	.19
Financial difficulties	19.1(17.5 to 20.8)	21.0(19.4 to 22.6)	-1.9(-4.2 to 0.4)	.11

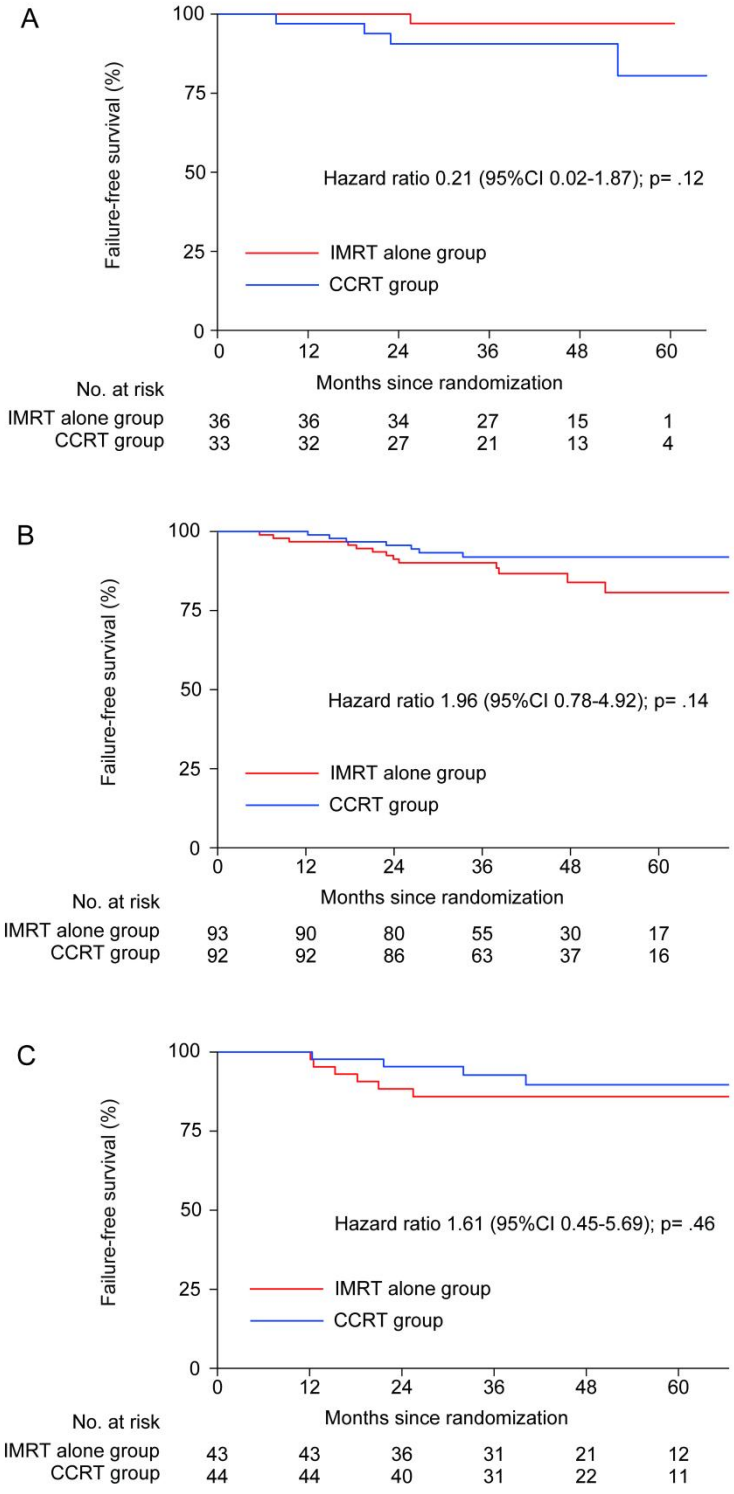
The health-related quality of life was evaluated by using a mixed effect model with scores assessed at each visit as a response value. The mean differences for the treatment represent the average difference in quality of-life scores between groups over the whole treatment period (6-7 weeks) adjusting for baseline scores, and the treatment effects were tested with the significance level set at 0.05.

EORTC QLQ-C30 were used to assess the QOL score. QoL data were collected using printed questionnaires before the initiation of treatment and thereafter once a week during the whole course of radiotherapy

CCRT = concurrent chemoradiotherapy

eFigure 1. Kaplan–Meier Analysis of Failure-Free Survival in the 2 Groups Stratified by Different Tumor Categories: (A) T1, (B) T2, (C)T3

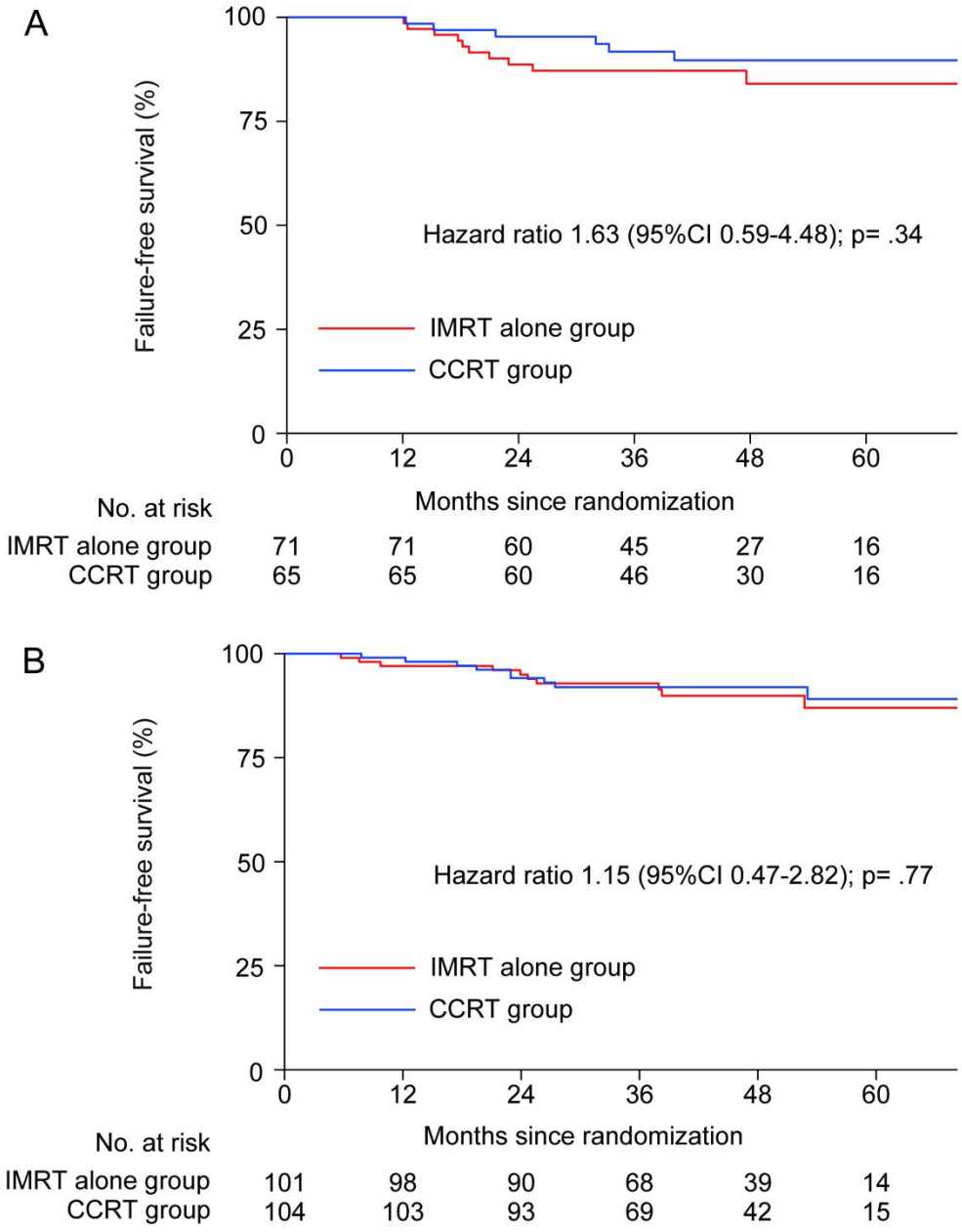
CCRT :concurrent chemoradiotherapy



eFigure 2. Kaplan–Meier Analysis of Failure-Free Survival in the 2 Groups Stratified by Different Node Categories: (A) N0, (B) N1

An unstratified Cox proportional-hazards model was used to calculate hazard ratios and 95% confidence intervals.

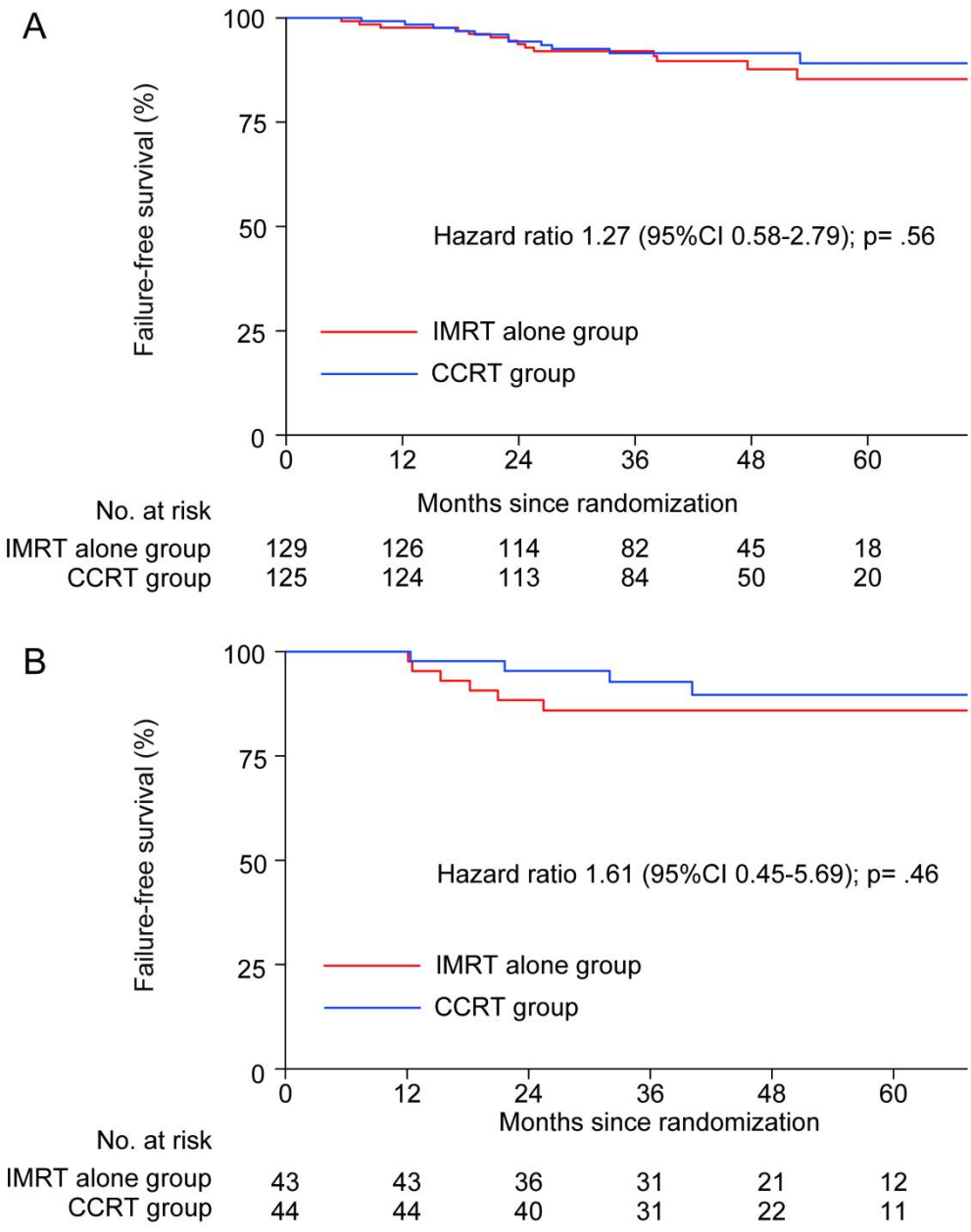
CCRT: concurrent chemoradiotherapy



eFigure 3. Kaplan–Meier analysis of Failure-Free Survival in the 2 Groups Stratified by Different Disease Stages: (A) stage II, (B) stage III

An unstratified Cox proportional-hazards model was used to calculate hazard ratios and 95% confidence intervals

CCRT: concurrent chemoradiotherapy



eFigure 4. Kaplan–Meier Analysis of Failure-Free Survival in the 2 Groups Stratified by Different Center

(A) Sun Yat-sen University Cancer Centre;(B)First People's Hospital of Foshan;

(C)Other three centers (The Wuzhou Red Cross Hospital, The fifth Affiliated Hospital of Sun Yat-sen University, Tongji Medical College Union Hospital of Huazhong University of Science and Technology)

CCRT: concurrent chemoradiotherapy

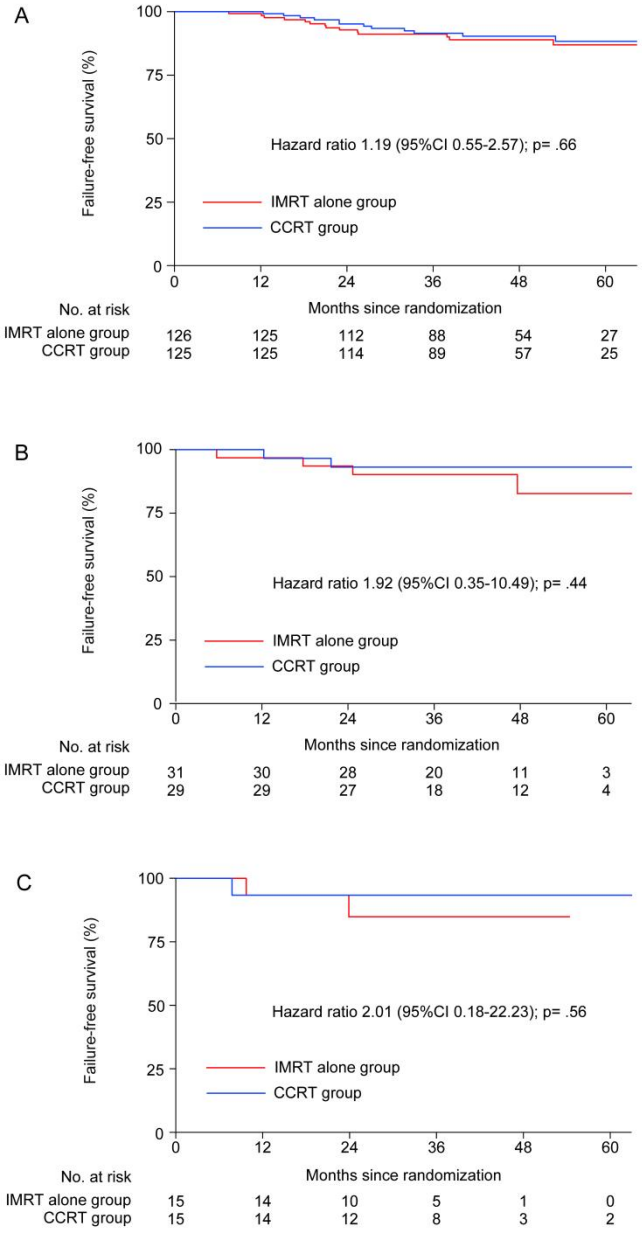


Figure S5. The results of QOL assessments evolved over time