Received: 25 June 2022 | Revised: 12 October 2022 | Accepted: 8 November 2022

DOI: 10.1002/lio2.980

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Short-term efficacy and long-term survival of nasopharyngeal carcinoma patients with radiographically visible residual disease following observation or additional intervention: A real-world study in China

Ying-Ying Huang MD[1] | Xun Cao MD[2] | Zhuo-Chen Cai MD[1] | Jia-Yu Zhou BS[1] | Xiang Guo MD, PhD[1] | Xing Lv MD, PhD[1]

[1]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, the State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China

[2]Department of Critical Care Medicine, Sun Yat-sen University Cancer Center, the State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China

Correspondence
Xing Lv and Xiang Guo, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, the State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China.
Email: lvxing@sysucc.org.cn and guoxiang@sysucc.org.cn

Funding information
Guangdong Basic and Applied Basic Research Foundation, Grant/Award Number: 2021A1515010118; National Natural Science Foundation of China, Grant/Award Number: 81872375, 82172863

Abstract

Background: To explore the short- and long-term outcomes in patients with nasopharyngeal carcinoma (NPC) with magnetic resonance imaging (MRI)-detected residual disease at 3 months post-treatment who received intervention either promptly (0 month) or following observation (after an additional 3 months).

Methods: A total of 272 patients with residual disease at 3 months post-treatment (observation [observation for additional 3 months]: 122, intervention [prompt intervention]: 150) were analyzed. Univariate and multivariate analyses were performed to examine the survival. Adverse events were analyzed in all patients.

Results: Patients in the observation group had a lower 3-year overall survival (77.1% vs. 85.2%), progression-free survival (10.2% vs. 18.1%), and locoregional relapse-free survival (10.2% vs. 20.6%) (all $p < .05$), but not distant metastasis-free survival (83.8% vs. 78.4%, $p = .189$), whereas patients in the intervention group achieved higher complete remission (CR) rates (43.3% vs. 21.2%, $p = .003$). Patients who achieved CR after prompt intervention had a better survival rate than those who achieved observation-CR or non-CR ($p < .001$). Multivariate analyses revealed that a wait-and-see policy was an independent prognostic factor for impaired survival ($p < .001$). No significant differences of acute or late toxicities were observed between the two groups.

Conclusions: Patients with NPC with MRI-detected residual disease 3 months post-radiotherapy should be encouraged to undergo prompt intervention rather than adopting a passive wait-and-see policy.

KEYWORDS
long-term survival, magnetic resonance imaging, nasopharyngeal carcinoma, residual disease, short-term efficacy

Ying-Ying Huang and Xun Cao contributed equally to this work.

1 | INTRODUCTION

As an epithelial malignancy arising from the nasopharynx, nasopharyngeal carcinoma (NPC) often manifests with invasive growth in the primary site and metastatic lymphadenopathy in the retropharyngeal lymph nodes (RLNs)/cervical lymph nodes (CLNs).[1] Although NPC is rare in most Western countries and Latin America, it was inversely estimated that over 70% ($n = 130{,}000$) of all cases worldwide were distributed in South China, Southeast Asia, and Northern Africa in 2018.[2–4]

Owing to the inherent anatomical constraints and hyperradiosensitivity of undifferentiated neoplastic cells, radical radiotherapy (RT) is the main treatment approach for NPC. As imaging equipment and RT technologies are improving, the implementation of intensity-modulated radiotherapy (IMRT) has led to satisfactory local control and long-term survival benefits in patients with NPC.[3,5] Owing to the infiltrative growth pattern of NPC, magnetic resonance imaging (MRI) with good soft tissue resolution is employed for assessing treatment efficacy.[6] Around 3%–13% of patients have local or regional persistent disease, 3–6 months after definitive RT.[7,8] On the one hand, due to the influences of volume reduction, structural changes, and the deep location of the tumor, a performing biopsy for residual disease is a difficult process.[9] Additionally, the pathological results have a certain false-negative rate. In most cases, oncologists rely on MRI to evaluate residual disease. On the other hand, the regression rate of gross tumors after RT on MRI differs between individuals (ranges from 0 to 12 months).[10] A significant portion of these patients with residual disease (34.9%) ultimately achieved full tumor regression after a prolonged time of observation or attenuated treatment.[10] Thus, commencing additional intervention too early may result in over-treatment in patients whose residual tumors may undergo spontaneous histologic remission slowly but firmly after a period of time. As arduous additional intervention results in more serious toxicities and complications to patients with residual disease, oncologists often struggle with whether to promptly provide invasive additional intervention to patients with diminishing residual disease at 3 months post-treatment. In addition, the long-term survival of patients with delayed spontaneous tumor regression (>3 months) and those whose tumors resolved after additional intervention were not compared.

To explore the short-term efficacy and long-term survival of patients with radiographically visible residual disease at 3 months after RT following observation (additional 3 months) or prompt intervention in the field of NPC, we conducted a retrospective, population-based, real-world study in an endemic area in China. By reporting the real survival trajectories of patients with residual disease at 3 months post-radiotherapy following observation (additional 3 months) or intervention, we aimed to reveal the clinical values of different forms of intervention in this group.

2 | PATIENTS AND METHODS

2.1 | Patients

A well-established big-data intelligence platform at Sun Yat-sen University Cancer Center (SYSUCC) was used to identify patients with residual, histologically proven, non-disseminated NPC diagnosed between January 2010 and December 2015. The inclusion criteria were as follows: (1) patients with histologically confirmed non-metastatic NPC without previous or concurrent malignant disease; (2) age ≥ 18 years old; (3) receipt of radical RT for the entire course at SYSUCC; (4) with sufficient clinical data; (5) regular follow-up with complete post-treatment examination, including nasopharyngoscopy, MRI of the nasopharynx and neck; (6) no evidence of distant metastasis during the first 3 months post-treatment; (7) no previous anticancer treatment; and (8) confirmation of radiographically visible residual disease at 3 months post-treatment. A total of 272 patients with MRI scan at diagnosis and MRI-detected residual but diminished NPC at 3 months after a complete course of full-dose irradiation ± chemotherapy at SYSUCC were enrolled in this study. All the patients were endemic cases and were restaged according to the eighth edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system. The Institutional Review Board of SYSUCC approved this study (B2021-215-01).

2.2 | MRI evaluation and diagnostic criteria

All patients underwent MRI scans of the nasopharynx and neck before and at the end of (±7 days) treatment, and at 3 and 6 months post-treatment. To ensure objectivity, two experienced radiologists specializing in head and neck cancers evaluated the images independently. Disagreements were resolved through discussion. The diagnostic criteria for residual disease on MR images were based on the criteria recommended by Lv et al.[9] Because most residual RLNs were unresectable within the time frame in this study, the residual diseases were classified into four types: residual disease in the primary site (residue T type), RLNs ± CLNs (residue N [with RLNs] type), CLNs (residue N [without RLNs] type) and concomitantly the primary site plus RLNs/CLNs (residue TN type). The classifications and stages of residual diseases on radiological images were defined based on the eighth edition of the UICC/AJCC staging system for uniformity (ycTNM) (Tables S1 and S2).

The maximum tumor diameters (MTD) of the primary tumor and metastatic RLNs/CLNs were measured separately on MR images. Tumor remission was evaluated based on the change between the total MTD (estimated as the sum of the MTD of the primary tumor and metastatic lymph nodes) of the post-treatment and pre-treatment statuses. Tumor remission was divided into four levels: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors 1.1 (2009).[11]

2.3 | Treatment and follow-up

All patients received radical RT using conventional RT or IMRT as primary treatment. The administration of induction and/or concurrent chemotherapy depended on the patient's physical status and disease

stage. Details about the RT techniques used at the SYSUCC were described in a previous study.[12] The target volume delineation was performed according to the International Commission on Radiological Units Guidelines. Doses to critical normal structures and plan evaluations were directed according to the Radiation Therapy Oncology Group guidelines. Gross tumors and RLNs were included within the primary gross target volume of our cancer center. The prescribed dose was 66.0–72.0 Gy for the primary tumor and 60.0–66.0 Gy for the involved CLNs, with fractions of 30–33.

Patients with residual disease were either observed for an additional 3 months or provided prompt intervention, at the physician's discretion, depending on the patient's physical status, initial tumor stage, tumor regression rate, and residual disease status. Patients were assessed every 3 months during the first 3 years, every 6 months during the next 2 years, and annually thereafter. The median follow-up duration of the entire group was 39.1 months (range, 4.9–153.2 months). Overall survival (OS) was the primary endpoint, which was measured from 3 months after the completion of RT to the date of death from any cause. Progression-free survival (PFS) was defined as the date from 3 months after the completion of RT to the date of the first occurrence of treatment failure or death from any cause, whichever occurred first. Locoregional relapse-free survival (LRRFS) was defined as the date from 3 months after the completion of RT to the date of the first occurrence of locoregional failure or death from any cause, whichever occurred first. Distant metastasis-free survival (DMFS) was recorded from 3 months after the completion of RT to the date of the first remote failure or death from any cause, whichever occurred first. Treatment-related adverse events are recorded according to the Common Terminology Criteria for Adverse Events grade.

2.4 | Statistical analysis

Pearson's χ^2 test or Fisher's exact test was used to assess categorical variables between groups. Differences in non-normally distributed variables between the groups were examined using the Mann–Whitney test. Actuarial survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses with the Cox proportional hazards model were used to identify significant independent prognostic factors using forward elimination (LR). Statistical analyses were performed using the SPSS statistical software version (version 26.0; IBM, Armonk, NY) and Prism analysis and the graphic software version 9.0.2 (GraphPad Software, San Diego, CA). A two-sided *p*-value of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics and prognosis

A total of 272 patients were detected with MRI-detected residual disease at 3 months after RT. Among them, 79 (29.0%) residual diseases were residue T, whereas 147 (54.1%) were residue N (42 with RLNs, 105 without RLNs), and 46 (16.9%) were residue TN (Table 1). Overall, 83 patients (30.5%) died, and 248 patients (91.2%) experienced treatment failure, including locoregional failure in 243 patients (89.3%) and distant metastasis in 58 patients (21.3%) (Table S3). For the entire cohort, the 3-year actuarial OS, PFS, LRRFS, and DMFS rates were 81.5%, 14.5%, 15.9%, and 80.8%, respectively.

3.2 | Treatments for patients with residual disease

Of the 272 patients, 122 (44.9%) received no further treatment 3 months post-radiotherapy in the observation group, whereas 150 (55.2%) received additional therapy (29 local therapy; 85 systemic therapy: 53 metronomic chemotherapy and 32 intravenous chemotherapy; and 36 comprehensive therapy: local therapy plus systemic therapy) in the intervention group (Table S4). The interval time of intervention was calculated from 3 months after the completion of the first-course RT to the first day of administration of adjuvant treatment, with a median value of 0.6 months.

3.3 | Short-term efficacy evaluation of patients

Three months after RT, the treatment efficacy of 272 patients was evaluated as PR based on the visual evaluation of tumor regression compared with the pretreatment disease shown on the MR images. Compared to the observation group, patients who accepted further intervention achieved an elevated CR rate (43.3% vs. 26.2%, $p = .003$). Similarly, increased trends were observed in both the overall response rate (ORR) and disease control rate (DCR) among the patients in the intervention group as compared with those in the observation group (ORR: 45.3% vs. 26.2%, $p = .001$; DCR: 47.3% vs. 30.3%, $p = .004$). Notably, patients who underwent local treatment had superior short-term clinical benefits compared with those who received systemic chemotherapy (CR rate: 61.5% vs. 29.4%, $p < .001$; ORR: 63.1% vs. 31.8%, $p < .001$; DCR: 63.1% vs. 35.3%, $p = .001$). In particular, patients receiving metronomic chemotherapy exhibited a rising trend in short-term clinical benefits compared with those who received intravenous chemotherapy (CR rate: 34.0% vs. 21.9%, $p = .236$; ORR: 37.7% vs. 21.9%, $p = .128$; DCR: 39.6% vs. 28.1%, $p = .283$) (Figure 1 and Table S5).

3.4 | Long-term survival of patients

The 3-year OS, PFS, and LRRFS rates for the four residual types differed significantly (OS, $p = .014$; PFS, $p = .001$; and LRRFS, $p = .002$; Figure 2A–C), whereas the 3-year DMFS rates were not significantly different ($p = .056$; Figure 2D). The residual type remained independent in the multivariate survival analyses of OS, PFS, and LRRFS (OS, $p = .046$; PFS, $p = .001$; and LRRFS, $p = .001$; Table 2).

Stratified by adjuvant treatment modality, the 3-year OS rates for the observation and intervention groups were 52.2% and 68.9%, respectively (hazard ratio [HR]: 1.86 [95% confidence interval [CI]:

TABLE 1 Clinical characteristics of 272 nasopharyngeal carcinoma patients with MRI-detected residual disease (3 months post-treatment) stratified by treatment mode

Characteristics		Observation group no. (%)	Intervention group no. (%)	χ^{2a}	P^a
Total	272	$n = 122$ (44.8)	$n = 150$ (55.2)		
Gender				1.95	0.162
Male	210	99 (81.2)	111 (74.0)		
Female	62	23 (18.8)	39 (26.0)		
Age (years)				0.52	0.472
≤45	154	72 (59.0)	82 (54.7)		
>45	118	50 (41.0)	68 (45.3)		
Histological type[b]				-	0.503
Keratinizing squamous cell carcinoma	2	0 (0.0)	2 (1.3)		
Nonkeratinizing squamous cell carcinoma	270	122 (100.0)	148 (98.7)		
T category[c]				-	0.797
T1	22	10 (8.1)	12 (8.0)		
T2	38	14 (11.5)	24 (16.0)		
T3	145	69 (56.6)	76 (50.7)		
T4	67	29 (23.8)	38 (25.3)		
N category[c]				-	0.147
N0	9	5 (4.1)	4 (2.7)		
N1	100	49 (40.2)	51 (34.0)		
N2	96	42 (34.4)	54 (36.0)		
N3	67	26 (21.3)	41 (27.3)		
Clinial stage[c]				-	0.596
I	2	1 (0.8)	1 (0.6)		
II	22	6 (4.9)	16 (10.7)		
III	126	65 (53.3)	61 (40.7)		
IV	122	50 (41.0)	72 (48.0)		
Pre-EBV DNA (copies/ml)				1.07	0.587
>2000	163	69 (56.6)	94 (62.7)		
≤2000	92	45 (36.9)	47 (31.3)		
NA	17	8 (6.5)	9 (6.0)		
Treatment regimen				4.34	0.227
RT alone	23	9 (7.4)	14 (9.3)		
CCRT	79	38 (31.1)	41 (27.3)		
IC + RT	49	16 (13.1)	33 (22.00)		
IC + CCRT	121	59 (48.4)	62 (41.4)		
Radiotherapy technique				5.47	0.019
IMRT	241	102 (83.6)	139 (92.7)		
2D-RT	31	20 (16.4)	11 (7.3)		
Dose to GTVnx (Gy)				0.21	0.650
≤70.0	254	113 (92.6)	141 (94.0)		
>70.0	18	9 (7.4)	9 (6.0)		
Dose to GTVnd (Gy)				0.12	0.729
≤68.0	199	88 (72.1)	111 (74.0)		
>68.0	73	34 (27.9)	39 (26.0)		
Residual tumor type				8.96	0.030
Residue T	79	45 (36.9)	34 (22.7)		

TABLE 1 (Continued)

Characteristics		Observation group no. (%)	Intervention group no. (%)	χ^{2a}	P^a
Residue N	147	61 (50.0)	86 (57.3)		
(with RLNs)	42	21 (17.2)	21 (14.0)		
(without RLNs)	105	40 (32.8)	65 (43.3)		
Residue TN	46	16 (13.1)	30 (20.0)		
Residue T category[d]				-	0.257
Residue T0	147	61 (50.0)	86 (57.3)		
Residue T1	8	3 (2.5)	5 (3.3)		
Residue T2	27	14 (11.5)	13 (8.7)		
Residue T3	48	24 (19.6)	24 (16.0)		
Residue T4	42	20 (16.4)	22 (14.7)		
Residue N category[e]				-	0.009
Residue N0	79	45 (36.9)	34 (22.7)		
Residue N1	135	56 (45.9)	79 (52.7)		
Residue N2	31	13 (10.7)	18 (12.0)		
Residue N3	27	8 (6.5)	19 (12.6)		
Residual tumor stage[f]				-	0.696
Residue I	6	3 (2.5)	3 (2.0)		
Residue II	126	57 (46.7)	69 (46.0)		
Residue III	71	33 (27.0)	38 (25.3)		
Residue IV	69	29 (23.8)	40 (26.7)		
Post-EBV DNA (copies/ml)				8.730	0.013
Undetectable	146	61 (50.00)	85 (56.7)		
Detectable	44	14 (11.5)	30 (20.0)		
NA	82	47 (38.5)	35 (23.3)		

Abbreviations: 2D-RT, two-dimensional radiotherapy; CCRT, concurrent chemoradiotherapy; GTVnd, gross tumor volume of metastatic cervical lymph nodes; GTVnx, gross tumor volume of nasopharynx; IC, induction chemotherapy; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; N, lymph node(s); NA, unknown; post-EBV DNA, three-month post-treatment plasma EBV DNA; pre-EBV DNA, pre-first routine treatment plasma Epstein–Barr virus deoxyribonucleic acid; RLNs, retropharyngeal lymph nodes; RT, radiotherapy; T, tumor.

[a]Pearson's χ^2 test or Fisher's exact test for categorical variables and Mann–Whitney U test for non-normally distributed variables were used to analyze patients' characteristics between the two groups.

[b]According to the World Health Organization (WHO) histologic classification (2005).

[c]All patients' diseases were re-staged according to the eighth edition of the American Joint Committee on Cancer (AJCC).

[d]The classification of residue T: residue T0 = no residual tumor identified in the primary tumor site; residue T1 = residual tumor confined to the nasopharynx, or extension to the oropharynx and/or nasal cavity without parapharyngeal involvement; residue T2 = residual tumor extension to the parapharyngeal space and/or adjacent soft tissue involvement; residue T3 = residual tumor with infiltration of bony structures at the skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses; residue T4 = residual tumor with intracranial extension.

[e]The classification of residue N: residue N0 = no residual tumor in RLNs or cervical lymph nodes (CLNs); residue N1 = unilateral or bilateral residual tumor in RLNs and/or unilateral residual tumor in CLNs, above the caudal border of the cricoid cartilage; residue N2 = bilateral residual tumor in CLNs, above the caudal border of the cricoid cartilage; residue N3 = unilateral or bilateral residual tumor in CLNs, and extension below the caudal border of the cricoid cartilage.

[f]The clinical stage of residual disease: residue I = residue T1N0M0; residue II = residue T2N0 and/or T0-2N1 M0; residue III = residue T3N0–1 and/or T0-3N2 M0; residue IV = residue T4N0–2 and/or T0-4N3 M0.

1.21–2.87], $p = .005$; Figure 3A). The 3-year PFS and LRRFS rates were also significantly different (PFS, 10.2% vs. 18.1%, HR: 1.29 [1.01–1.67], $p = .041$; LRRFS, 10.2% vs. 20.6%, HR: 1.39 [1.08–1.80], $p = .009$; Figure 3B–C). However, the 3-year DMFS rate did not differ significantly ($p = .189$; Figure 3D). In Cox proportional hazards analyses, the adjuvant treatment mode was an independent prognostic factor for OS (HR: 1.92 [1.23–2.99], $p = .004$), PFS (HR: 1.34 [1.03–1.73], $p = .028$), and LRRFS (HR: 1.45 [1.12–1.89], $p = .006$) (Table 2).

Furthermore, we compared the survival curves of patients according to treatment modality in detail. The 3-year OS rates for the observation, local therapy, comprehensive therapy, metronomic

chemotherapy, and intravenous groups were 84.4%, 88.1%, 96.4%, 92.0%, and 67.7%, respectively ($p = .016$; Figure 4A). Additionally, the 3-year PFS and LRRFS rates were significantly different between groups (PFS, 10.6% vs. 46.0% vs. 20.5% vs. 10.5% vs. 8.7%, $p < .001$; LRRFS, 10.4% vs. 53.2% vs. 29.4% vs. 12.6% vs. 10.6%, $p < 0.001$; Figure 4B–C), respectively. The 3-year DMFS rates were 88.9%, 60.8%, 83.9%, 90.3%, and 73.7% ($p = .594$; Figure 4D).

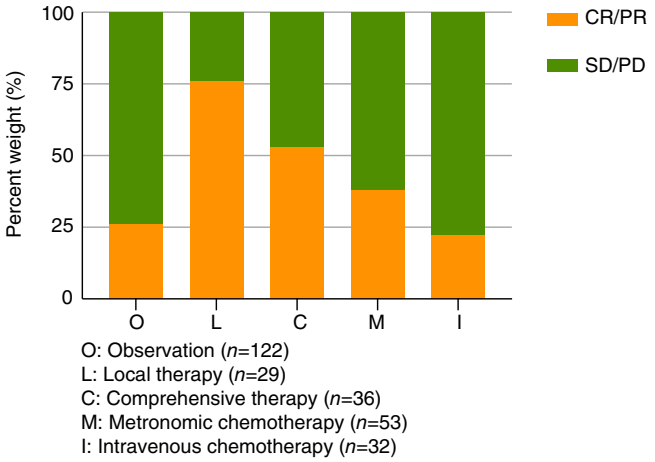

FIGURE 1 Comparison of the short-term clinical efficacy following observation (additional 3 months) or intervention among patients with 3 months post-treatment MRI-detected residual NPC. CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

According to the short-term efficacy in patients with residual disease after observation or intervention (median, 10.6 months; interquartile range [IQR], 7.7–14.6 months), they were subdivided into three subgroups: 32 observation-CR patients, 65 intervention-CR patients, and 175 non-CR patients. The 3-year OS rates for three subgroups were 93.2%, 96.2%, and 73.5% ($p < .001$; Figure 5A), respectively. The 3-year PFS, LRRFS, and DMFS rates also differed significantly (PFS, 25.0% vs. 36.3% vs. 4.4%, $p < .001$; LRRFS, 25.0% vs. 36.3% vs. 6.6%, $p < .001$; and DMFS, 93.1% vs. 96.6% vs. 72.1%, $p < .001$; Figure 5B–D).

3.5 | Treatment toxicities

The type and frequency of treatment toxicities are summarized in Table S6. During the available follow-up period, dermatitis was the most common grade 1–2 acute adverse event (90/122 [73.8%] in the observation group; 112/150 [74.7%] in intervention group, $p = .866$), followed by xerostomia (73/122 [59.8%] in the observation group;

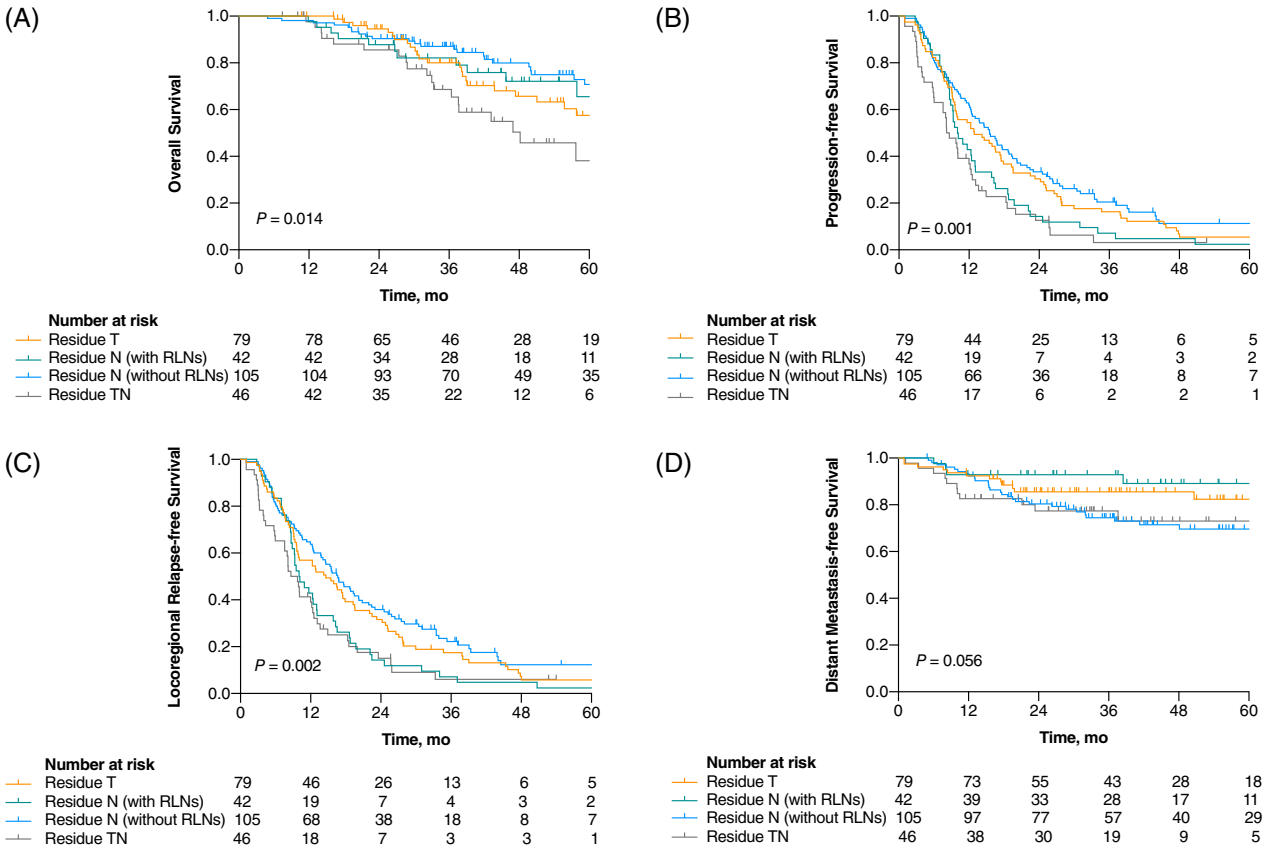

FIGURE 2 Kaplan–Meier curves for (A) overall survival, (B) progression-free survival, (C) locoregional relapse-free survival, and (D) distant metastasis-free survival in patients with MRI-detected residual disease at 3 months post-treatment stratified by residual tumor type. mo, month; N, lymph node(s); RLNs, retropharyngeal lymph nodes; T, tumor; TN, tumor and lymph node(s).

TABLE 2 Cox proportional hazards analyses identified prognostic variables with significant value in the 272 nasopharyngeal carcinoma patients with MRI-detected residual disease

Endpoint	Variables[a]	HR	95% CI	*p*
OS	Treatment (observation)	1.92	1.23–2.99	.004
	Residue type (residue T, reference)			.046
	Residue N (with RLNs)	1.18	0.56–2.51	.662
	Residue N (without RLNs)	0.93	0.53–1.64	.803
	Residue TN	2.06	1.13–3.74	.018
	Residual tumor stage (residue III–IV)	1.70	1.02–2.75	.032
PFS	Treatment (observation)	1.34	1.03–1.73	.028
	Residue type (residue T, reference)			.001
	Residue N (with RLNs)	1.44	0.97–2.12	.069
	Residue N (without RLNs)	0.91	0.67–1.25	.578
	Residue TN	1.83	1.24–2.70	.002
LRRFS	Treatment (observation)	1.45	1.12–1.89	.006
	Residual tumor type (residue T, reference)			.001
	Residue N (with RLNs)	1.53	1.04–2.27	.033
	Residue N (without RLNs)	0.92	0.67–1.27	.613
	Residue TN	1.75	1.18–2.59	.005
DMFS	NA	NA	NA	NA

Abbreviations: CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; LRRFS, locoregional relapse-free survival; MRI, magnetic resonance imaging; NA, unknown; OS, overall survival; PFS, progression-free survival.

[a]The following variables were included in the Cox proportional hazards model multivariate analysis with forward elimination (LR): age (≤ 45 vs. > 45 years), gender (male vs. female), residual tumor type (residue T vs. residue N [with RLNs] vs. residue N [without RLNs] vs. residue TN), residual tumor stage (residue I–II vs. III–IV) and treatment (observation vs. intervention).

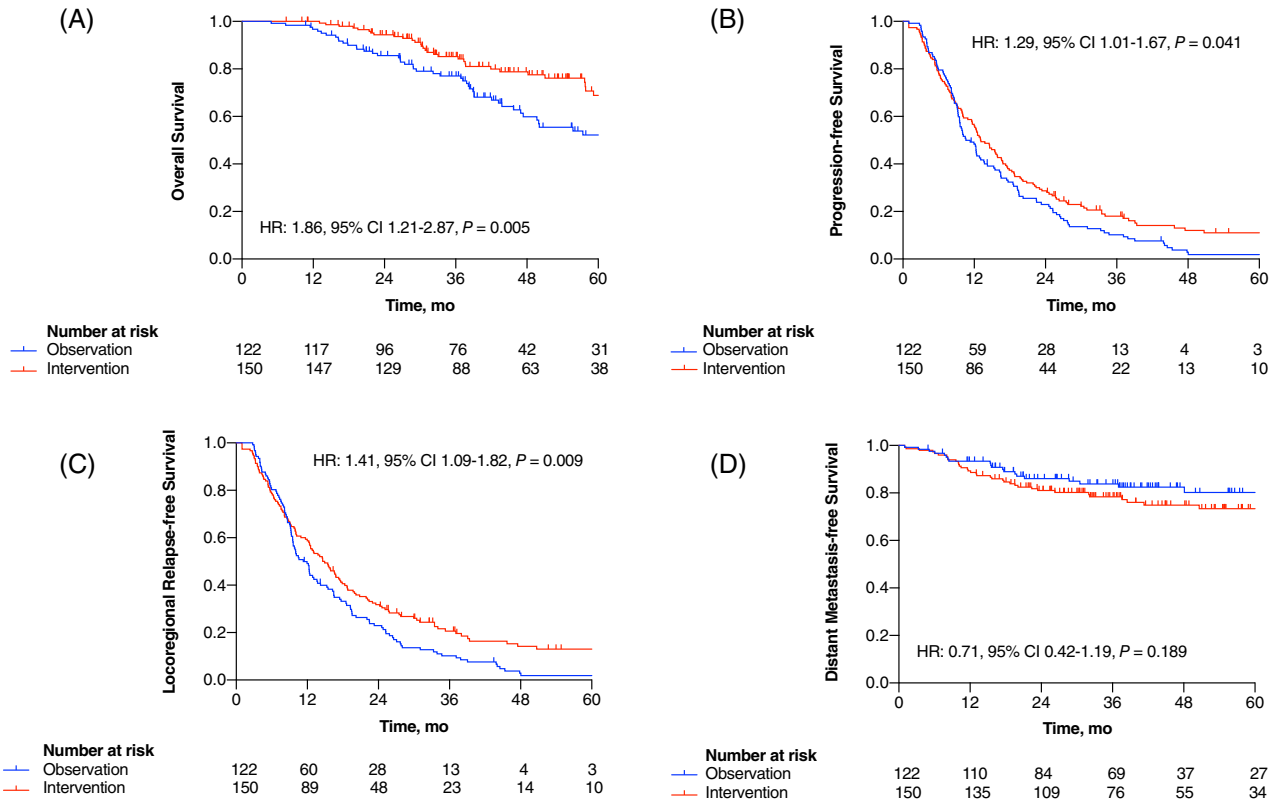

FIGURE 3 Kaplan–Meier curves for (A) overall survival, (B) progression-free survival, (C) locoregional relapse-free survival, and (D) distant metastasis-free survival in patients with NPC residual disease detected at 3 months post-treatment MRI who received observation (additional 3 months) or prompt intervention. CI, confidential interval; HR, hazard ratio; mo, month.

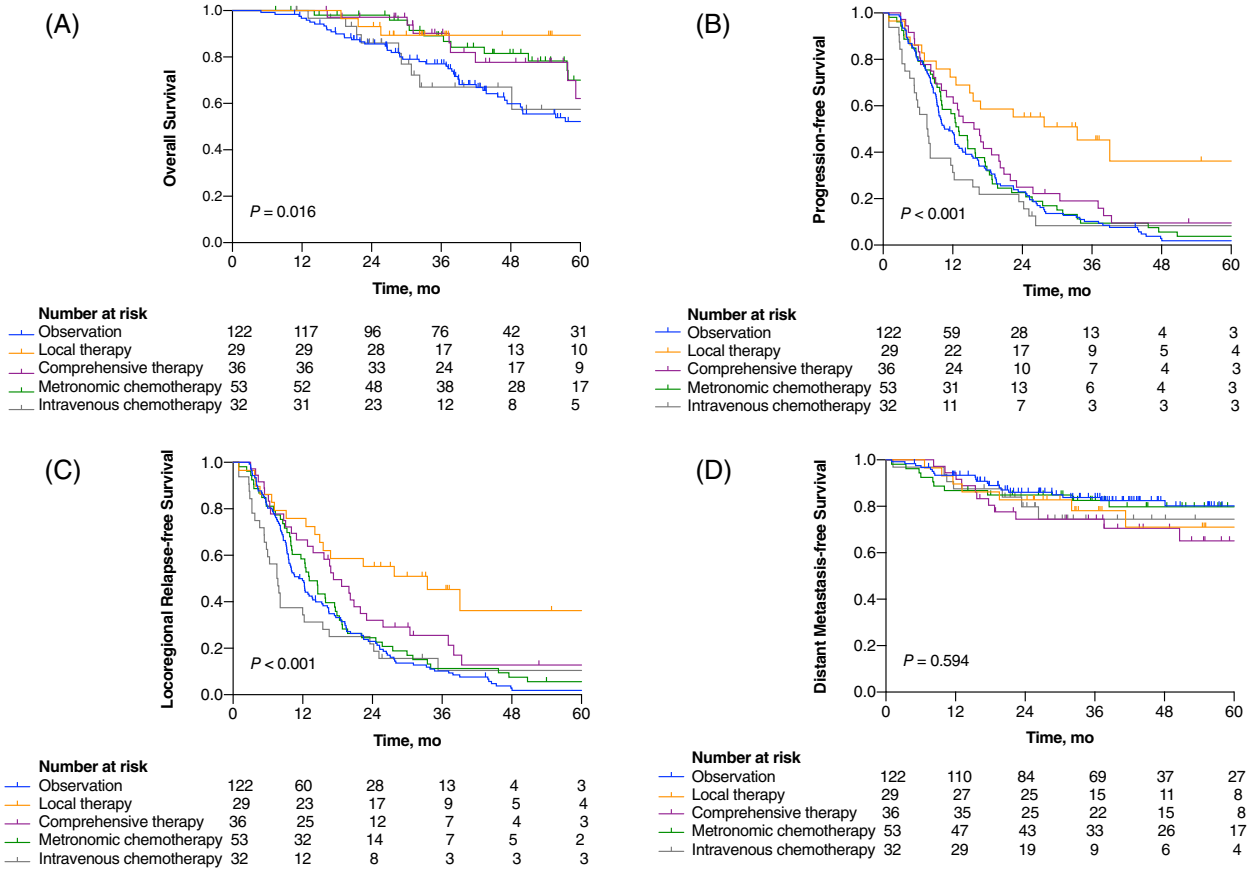

FIGURE 4 Kaplan–Meier curves for (A) overall survival, (B) progression-free survival, (C) locoregional relapse-free survival, and (D) distant metastasis-free survival in patients with 3 months post-treatment MRI-detected NPC residual disease who received observation (additional 3 months), local therapy, comprehensive therapy, oral chemotherapy, or intravenous chemotherapy. mo, month.

95/150 [63.3%] in the intervention group, $p = .555$) in both groups. Overall, xerostomia, neck fibrosis, and hearing impairment were the most commonaly observed grade 1–2 late adverse events in both groups, whereas the incidences of acute and late grade 3–4 adverse events were relatively low. No significant differences of acute or late toxicities were observed between the two groups.

4 | DISCUSSION

Despite the innovation of RT technologies, 3%–13% of patients with NPC experience locoregional residual disease after definitive irradiation.[13–16] Over the past two decades, considerable effort has been made to investigate the prognostic value of[9,17–19] and forecast the occurrence of residual disease as well as their preventive effects,[18] compare the capability to diagnose and differentiate residual disease among available medical procedures,[6,15] or develop predictive models for prognostic stratification and risk adjustment[9] in this field. However, an optimal adjuvant treatment for residual NPC that effectively improves both short- and long-term benefits remains unexplored. To the best of our knowledge, this study is the first to report the real survival trajectories of patients with radiographically visible residual disease at 3 months post-treatment on MRI for NPC, following observation for an additional 3 months or prompt intervention. Moreover, we compared the clinical benefits of observation and intervention, in terms of short-term efficacy and long-term survival, in patients with residual NPC.

Detecting residual tumors in a timely and precise manner is necessary to provide prompt additional treatment.[20–25] Based on a prospective study investigating the time course of tumor regression in patients with NPC residual lesions, performing an imaging evaluation at 3 months post-treatment was dependable.[26] Currently, MRI has been regarded as the best imaging procedure due to its greater overall accuracy in detecting residual foci.[6] When residual lesions can be detected with high sensitivity, the nature of the residual disease is difficult to be clarified. The feasibility of biopsy in diagnosing residual foci has been overshadowed in clinical practice because of its invasive properties or the hard-to-reach location of residual lesions.[26–29] In addition, the salvage treatments for persistent tumors recommended in the current guidelines are aggressive, along with inevitable complications. Oncologists often struggle to promptly provide additional interventions to patients with unclarified residual diseases.

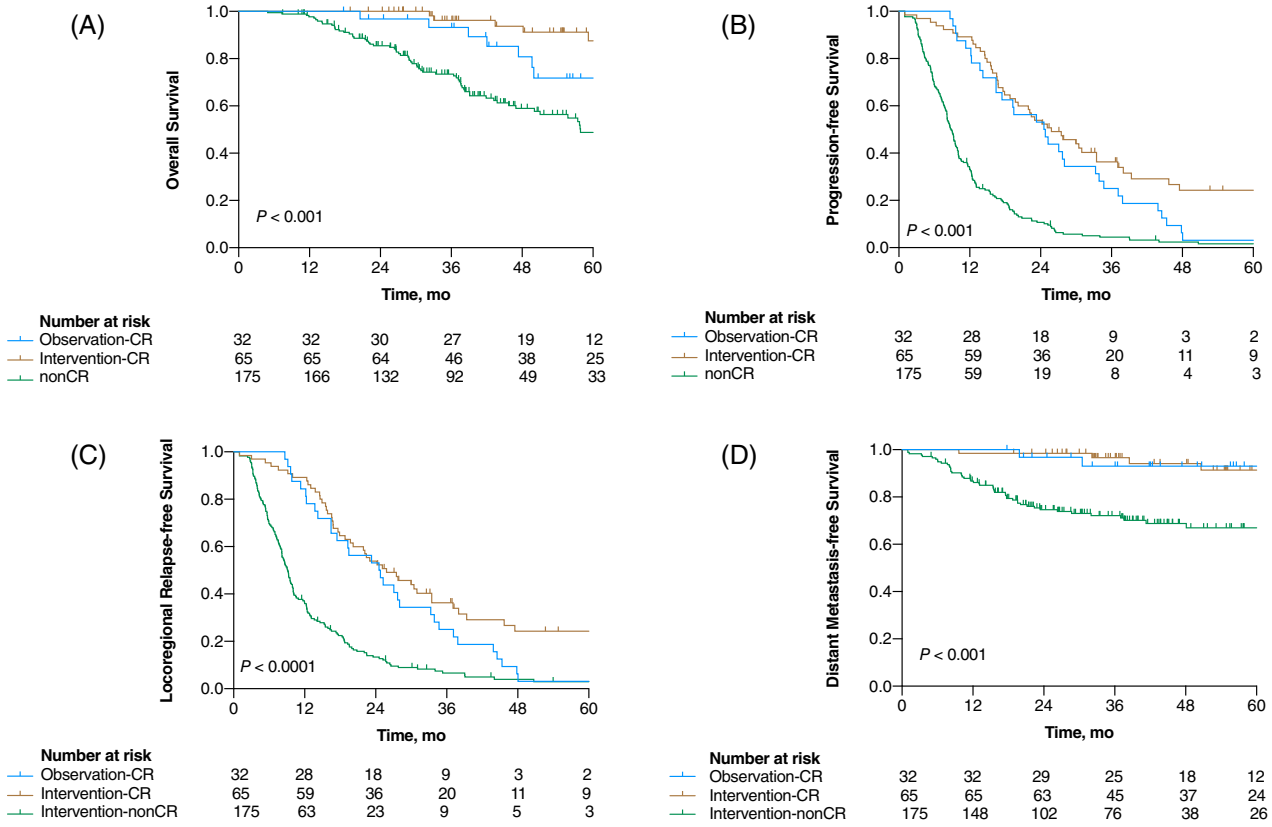

FIGURE 5 Kaplan–Meier curves for (A) overall survival, (B) progression-free survival, (C) locoregional relapse-free survival, and (D) distant metastasis-free survival in patients with NPC residual disease with CR and non-CR detected 3 months post-treatment after observation (additional 3 months) or prompt intervention. CR, complete remission; mo, month; non-CR, non-complete remission.

In our study, oncologists were more aggressive in the treatment of patients with residual disease, both at the primary tumor site and in metastatic CLNs. As observed in our study, those patients with a residual TN type exhibited inferior survival in OS, PFS, LRRFS, or DMFS than those with the other three types, indicating a possible correlation between the degrees of residual disease. In the same vein, patients with advanced residual disease in CLNs are more likely to receive prompt intervention and can be explained by the fact that neck dissection is more convenient and effective for patients with residual CLNs. As more patients with residual CLNs were treated in the intervention arm, a higher incidence of neck fibrosis was observed compared with the observation group; however, there was no significance. However, due to the limited indications and difficulty of performing local therapy in the primary site, oncologists were irresolute whether to provide intervention to these patients. Thus, there was no distribution difference in the two groups for patients with residual disease at the primary tumor site.

Clinically, gross tumor regression after RT is an independent prognostic factor in patients with NPC.[30] In our study, patients who achieved CR exhibited superior survival compared with those who did not achieve CR. Our results further indicated that even for patients with residual disease, timely and effective strengthening of interventions might reverse poor outcomes. On the other hand, the 3-year OS, PFS, LRRFS, and DMFS rates for the patients who achieved observation-CR and intervention-CR were 93.2% and 96.2%, 25.0% and 36.3%, 25.0% and 36.3%, and 93.1% and 96.6%, respectively. These results demonstrated that patients with observation-CR have inferior outcomes compared with those with intervention-CR. Although there may be a few "negative" cases, we speculate that there may be an ambush of residual malignant cell populations within the residual lesions, which requires further and prompt intervention.

By stratifying patients into subgroups by remedies, patients with residual disease were more likely to reveal elevated CR rates and have superior OS, PFS, and LRRFS after receiving local therapy or comprehensive therapy with curative intent. In other words, the effect of a straightforward elimination method for localized macro-residues surpassed that of a relatively moderate systemic treatment. Admittedly, the magnitude of benefit was maximized by strictly controlled indications for local therapy. However, the results suggest that even if the residual disease is not locally treatable at the outset, clinicians should localize the foci through systemic treatment. Once a broad residual disease is localized, clinicians should provide patients with local therapy. Furthermore, the survival curves in the DMFS plot demonstrated that local treatment alone might not be sufficient to eradicate subclinical micrometastases that are not

detected by current imaging procedures. Previous studies have suggested that systemic chemotherapy can improve survival and reduce the risk of distant metastasis in NPC.[31,32] Oncologists and patients should not be concerned only with the elimination of locoregional residual diseases; once the local lesions are well controlled, long-term survival benefits should be pursued through further systemic therapy with sufficient intensity.

Similar to the results of other studies investigating high-risk NPC, patients with residual disease who underwent metronomic chemotherapy exhibited improved OS and reduced risk of distant metastasis when compared with those in the observation group only.[33–36] Another unique result of this study was that the clinical benefits to patients in the metronomic chemotherapy group were equivalent to those in the intravenous chemotherapy group. There are two possible explanations for this observation. Although NPC is a type of cancer with initial chemosensitivity to platinum-based regimens, a study has revealed that the use of a conventional strategy of platinum-based regimens failed to demonstrate any survival benefit in the adjuvant treatment mode for NPC.[37] Similarly, residual tumors may respond to fluorouracil metronomic chemotherapy after the initial platinum-based regimen (93.8% of patients received platinum-based regimen in the intravenous chemotherapy group). Moreover, owing to the necessary intensity of the intravenous chemotherapy regimen, a prolonged break of at least 21 days is required between successive cycles of therapy. Additionally, poor tolerability and compliance with burdensome intravenous chemotherapy may partly contribute to inferior efficacy.[37–39] In part, a prolonged interval between drug administration allows for the repair and recovery of tumor blood vessels as well as the regeneration of tumor deposits.[40] Considering the available evidence, the use of continuous, break-free, low-dose oral metronomic chemotherapy may serve as a promising therapeutic option with comparable survival benefits to intravenous chemotherapy for patients with residual NPC.

The retrospective nature of this study may cause inevitable bias encompassing patient selection, diagnosis, and efficacy evaluation. Our diagnostic criteria for residual tumors were based on MRI observations, which could be subjective, and some RT-induced foci are difficult to differentiate without histopathological verification. Thus, certain false-negative and false-positive probabilities cannot be circumvented. To reduce potential bias, two professional radiologists independently assessed all cases, with discrepancies settled by consensus. Additionally, more patients with residual CLNs were treated in the intervention arm, which may have led to a sampling bias. However, the number of patients with residual disease in the cervical regions is a result of improved regional control due to the accessibility of anatomical positions and the exquisite workmanship of neck dissection with strictly controlled indications; this is a veritable phenomenon observed in medical care. Therefore, our results encourage customized treatments on a patient-by-patient basis. Second, the number of samples enrolled in this study was limited because of the advanced locoregional control rate of IMRT. Third, this study was a single-institution analysis of an endemic region. Larger-scale randomized prospective clinical studies are required to further reduce the presence of bias.

5 | CONCLUSION

After comparison of treatment modalities, patients who achieved CR via intervention exhibited superior survival benefits with acceptable toxicities than patients who achieved delayed spontaneous CR (>3 months). In conclusion, patients with MRI-detected residual NPC should be encouraged to receive additional intervention instead of observation for 3 months. Prospective studies investigating treatment strategies for patients with residual NPC are warranted.

ACKNOWLEDGMENT

This study was supported by grants from the National Natural Science Foundation of China, Grant/Award Numbers: 81872375 and 82172863; Guangdong Basic and Applied Basic Research Foundation, Grant/Award Number: 2021A1515010118.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn) with approval RDD number (RDDA2021002083). All data will be shared upon request to the corresponding author.

ORCID

Ying-Ying Huang https://orcid.org/0000-0003-4837-731X

REFERENCES

1. Grégoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol*. 2014;110(1):172-181. doi:10.1016/j.radonc.2013.10.010
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492
3. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *The Lancet*. 2019;394(10192):64-80. doi:10.1016/S0140-6736(19)30956-0
4. Li K, Lin GZ, Shen JC, Zhou Q. Time trends of nasopharyngeal carcinoma in urban Guangzhou over a 12-year period (2000–2011): declines in both incidence and mortality. *Asian Pac J Cancer Prev*. 2014;15(22):9899-9903. doi:10.7314/APJCP.2014.15.22.9899
5. Lee AWM, Ng WT, Chan LLK, et al. Evolution of treatment for nasopharyngeal cancer––success and setback in the intensity-modulated radiotherapy era. *Radiother Oncol*. 2014;110(3):377-384. doi:10.1016/j.radonc.2014.02.003
6. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of

MR imaging and FDG PET/CT. *Radiology*. 2008;249(1):203-211. doi:10.1148/radiol.2491071753
7. Mao YP, Tang LL, Chen L, et al. Prognostic factors and failure patterns in non-metastatic nasopharyngeal carcinoma after intensity-modulated radiotherapy. *Chin J Cancer*. 2016;35(1):103. doi:10.1186/s40880-016-0167-2
8. Zhang MX, Li J, Shen GP, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: a 10-year experience with a large cohort and long follow-up. *Eur J Cancer*. 2015;51(17):2587-2595. doi:10.1016/j.ejca.2015.08.006
9. Lv JW, Zhou GQ, Li JX, et al. Magnetic resonance imaging-detected tumor residue after intensity-modulated radiation therapy and its association with post-radiation plasma Epstein-Barr virus deoxyribonucleic acid in nasopharyngeal carcinoma. *J Cancer*. 2017;8(5):861-869. doi:10.7150/jca.17957
10. Meng K, Tey J, Ho FCH, Asim H, Cheo T. Utility of magnetic resonance imaging in determining treatment response and local recurrence in nasopharyngeal carcinoma treated curatively. *BMC Cancer*. 2020;20(1):193. doi:10.1186/s12885-020-6664-3
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *JNCI: Journal of the National Cancer Institute*. 2000;92(3):205-216. doi:10.1093/jnci/92.3.205
12. Zhao C, Han F, Lu LX, et al. Intensity modulated radiotherapy for local-regional advanced nasopharyngeal carcinoma. *Ai Zheng*. 2004;23(11 Suppl):1532-1537.
13. Yau TK, Sze WM, Lee WM, et al. Effectiveness of brachytherapy and fractionated stereotactic radiotherapy boost for persistent nasopharyngeal carcinoma. *Head Neck*. 2004;26(12):1024-1030. doi:10.1002/hed.20093
14. Zheng XK, Chen LH, Chen YQ, Deng XG. Three-dimensional conformal radiotherapy versus intracavitary brachytherapy for salvage treatment of locally persistent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2004;60(1):165-170. doi:10.1016/j.ijrobp.2004.02.059
15. Liu SL, Tang LQ, Chen QY, et al. The prognosis of neck residue nasopharyngeal carcinoma (NPC) patients: results from a case-cohort study. *J Cancer*. 2018;9(10):1765-1772. doi:10.7150/jca.24573
16. Chen J, Huang WX, Wei W, et al. Surgical management for residual or recurrent diseases in the neck after radiotherapy in nasopharyngeal carcinoma. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2012;47(3):180-184.
17. He Y, Zhou Q, Shen L, et al. A retrospective study of the prognostic value of MRI-derived residual tumors at the end of intensity-modulated radiotherapy in 358 patients with locally-advanced nasopharyngeal carcinoma. *Radiat Oncol*. 2015;10:89. doi:10.1186/s13014-015-0401-0
18. Li WZ, Liu GY, Lin LF, et al. MRI-detected residual retropharyngeal lymph node after intensity-modulated radiotherapy in nasopharyngeal carcinoma: prognostic value and a nomogram for the pretherapy prediction of it. *Radiother Oncol*. 2020;145:101-108. doi:10.1016/j.radonc.2019.12.018
19. Mäntylä M, Kortekangas AE, Valavaara RA, Nordman EM. Tumour regression during radiation treatment as a guide to prognosis. *Br J Radiol*. 1979;52(624):972-977. doi:10.1259/0007-1285-52-624-972
20. Kwong DL, Wei WI, Cheng AC, et al. Long term results of radioactive gold grain implantation for the treatment of persistent and recurrent nasopharyngeal carcinoma. *Cancer*. 2001;91(6):1105-1113.
21. Teo P, Leung SF, Choi P, Lee WY, Johnson PJ. Afterloading radiotherapy for local persistence of nasopharyngeal carcinoma. *Br J Radiol*. 1994;67(794):181-185. doi:10.1259/0007-1285-67-794-181
22. Wei WI, Ho CM, Yuen PW, Fung CF, Sham JST, Lam KH. Maxillary swing approach for resection of tumors In and around the nasopharynx. *Archives of Otolaryngology - Head and Neck Surgery*. 1995;121(6):638-642. doi:10.1001/archotol.1995.01890060036007
23. Liu J, Yu H, Sun X, et al. Salvage endoscopic nasopharyngectomy for local recurrent or residual nasopharyngeal carcinoma: a 10-year experience. *Int J Clin Oncol*. 2017;22(5):834-842. doi:10.1007/s10147-017-1143-9
24. Zhang L, Zhu Y x, Wang Y, Huang C p, Wu Y, Ji Q h. Salvage surgery for neck residue or recurrence of nasopharyngeal carcinoma: a 10-year experience. *Ann Surg Oncol*. 2011;18(1):233-238. doi:10.1245/s10434-010-1292-9
25. Chen JY, Zhang L, Ji QH, et al. Selective neck dissection for neck residue of nasopharyngeal carcinoma: a prospective study. *J Craniomaxillofac Surg*. 2015;43(8):1571-1576. doi:10.1016/j.jcms.2015.06.037
26. Kwong DL, Nicholls J, Wei WI, et al. The time course of histologic remission after treatment of patients with nasopharyngeal carcinoma. *Cancer*. 1999;85(7):1446-1453. doi:10.1002/(sici)1097-0142(19990401)85:73.0.co;2-3
27. Ng SH, Chang JTC, Ko SF, Wan YL, Tang LM, Chen WC. MRI in recurrent nasopharyngeal carcinoma. *Neuroradiology*. 1999;41(11):855-862. doi:10.1007/s002340050857
28. Chan JY, Chan RC, Chow VL, To VS, Wei WI. Efficacy of fine-needle aspiration in diagnosing cervical nodal metastasis from nasopharyngeal carcinoma after radiotherapy. *Laryngoscope*. 2013;123(1):134-139. doi:10.1002/lary.23373
29. He LJ, Xie C, Li Y, et al. Ultrasound-guided fine needle aspiration of retropharyngeal lymph nodes after radiotherapy for nasopharyngeal carcinoma: a novel technique for accurate diagnosis. *Cancer Commun*. 2018;38(1):20. doi:10.1186/s40880-018-0286-z
30. Liang SB, Zhang N, Chen DM, et al. Prognostic value of gross tumor regression and plasma Epstein Barr virus DNA levels at the end of intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma. *Radiother Oncol*. 2019;132:223-229. doi:10.1016/j.radonc.2018.10.010
31. Liu SL, Sun XS, Yan JJ, et al. Optimal cumulative cisplatin dose in nasopharyngeal carcinoma patients based on induction chemotherapy response. *Radiother Oncol*. 2019;137:83-94. doi:10.1016/j.radonc.2019.04.020
32. Li WF, Chen NY, Zhang N, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of phase 3 randomized controlled trial. *Int J Cancer*. 2019;145(1):295-305. doi:10.1002/ijc.32099
33. Chen YP, Liu X, Zhou Q, et al. Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. *Lancet*. 2021;398:303-313. doi:10.1016/S0140-6736(21)01123-5
34. Twu CW, Wang WY, Chen CC, et al. Metronomic adjuvant chemotherapy improves treatment outcome in nasopharyngeal carcinoma patients with postradiation persistently detectable plasma Epstein-Barr virus deoxyribonucleic acid. *Int J Radiat Oncol Biol Phys*. 2014;89(1):21-29. doi:10.1016/j.ijrobp.2014.01.052
35. Liu YC, Wang WY, Twu CW, et al. Prognostic impact of adjuvant chemotherapy in high-risk nasopharyngeal carcinoma patients. *Oral Oncol*. 2017;64:15-21. doi:10.1016/j.oraloncology.2016.11.008
36. Chen J, Huang W, Ho C, Chao T, Lee J. Evaluation of oral tegafur-uracil as metronomic therapy following concurrent chemoradiotherapy in patients with non-distant metastatic TNM stage IV nasopharyngeal carcinoma. *Head Neck*. 2019;41(11):3775-3782. doi:10.1002/hed.25904
37. Chan ATC, Hui EP, Ngan RKC, et al. Analysis of plasma Epstein-Barr virus DNA in nasopharyngeal cancer after chemoradiation to identify high-risk patients for adjuvant chemotherapy: a randomized controlled trial. *J Clin Oncol*. 2018;36(31):3091-3100. doi:10.1200/JCO.2018.77.7847

38. Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2012;13(2):163-171. doi:10.1016/S1470-2045(11)70320-5
39. Chen L, Hu CS, Chen XZ, et al. Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase 3 multicentre randomised controlled trial. *Eur J Cancer*. 2017;75:150-158. doi:10.1016/j.ejca.2017.01.002
40. Chee J, Ting Y, Ong YK, Chao SS, Loh KS, Lim CM. Relapse status as a prognostic factor in patients receiving salvage surgery for recurrent or residual nasopharyngeal cancer after definitive treatment. *Head Neck*. 2016;38(9):1393-1400. doi:10.1002/hed.24451

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Huang Y-Y, Cao X, Cai Z-C, Zhou J-Y, Guo X, Lv X. Short-term efficacy and long-term survival of nasopharyngeal carcinoma patients with radiographically visible residual disease following observation or additional intervention: A real-world study in China. *Laryngoscope Investigative Otolaryngology*. 2022;7(6):1881-1892. doi:10.1002/lio2.980