Original Article

Clinical Outcomes of Carbon-Ion Radiotherapy for Patients With Locoregionally Recurrent Nasopharyngeal Carcinoma

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BACKGROUND: Reirradiation for locoregionally recurrent nasopharyngeal carcinoma (LR-NPC) after high-dose radiotherapy (RT) is challenging and usually is associated with poor survival and severe toxicities. Because of its physical and biological advantages over photon-beam RT, carbon-ion RT (CIRT) could be a potential treatment option for patients with LR-NPC. **METHODS:** Patients with LR-NPC who underwent salvage therapy using CIRT at the Shanghai Proton and Heavy Ion Center between May 2015 and June 2019 were analyzed. CIRT doses were 50 to 69 gray equivalent (GyE) (2.0-3.0 GyE per fraction). Overall survival (OS), local control, regional control, distant control, and acute and late toxicities were analyzed. Univariable and multivariable analyses of OS and local control were performed using the Cox regression model. **RESULTS:** Among the 206 patients included, 139 patients (67.5%) had recurrent American Joint Committee on Cancer stage III or stage IV disease. With a median follow-up of 22.8 months, the 2-year OS, local control, regional control, and distant control rates were 83.7%, 58.0%, 87.3%, and 94.7%, respectively. Multivariable analysis revealed that older age ($P = .017$) was predictive of worse OS, whereas a larger tumor volume ($P = .049$) and a lower biological equivalent dose ($P = .029$) were associated with inferior local control. No patient developed an acute toxicity of ≥grade 3 during CIRT. Severe (≥grade 3) late toxicities included temporal lobe necrosis (0.97%), cranial neuropathy (0.49%), hearing loss (1.46%), xerostomia (0.49%), and mucosal necrosis (16.02%) (toxicities were graded using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria). **CONCLUSIONS:** Salvage treatment using CIRT is efficacious for patients with LR-NPC and its toxicities are acceptable. CIRT may improve the survival and toxicity profiles substantially for patients with LR-NPC compared with the reported results after photon-based intensity-modulated RT. ***Cancer* 2020;126:5173-5183**.

KEYWORDS: carbon-ion radiotherapy (CIRT), disease control, locoregionally recurrent nasopharyngeal carcinoma, survival, toxicities.

INTRODUCTION

Despite the prevailing use of intensity-modulated radiotherapy (IMRT) in the management of patients with nasopharyngeal carcinoma (NPC), local recurrence remains one of the most important modes of treatment failure. Overall, 10% to 15% of patients will fail locally after undergoing definitive RT.[1] Various strategies including surgery, stereotactic radiosurgery, or brachytherapy have been attempted to salvage patients with locally recurrent NPC (LR-NPC); however, to the best of our knowledge, their uses are limited to disease foci of small volume,[2-4] whereas chemotherapy usually is reserved for patients who are not candidates for definitive local treatment. Reirradiation with IMRT remains the mainstay of treatment of patients with LR-NPC. Nevertheless, the outcome for these patients is dismal. The 2-year overall survival (OS) rate ranges from approximately 60% to 70% after salvage IMRT and is approximately 40% in patients with locally advanced disease at the time of recurrence.[5-7]

Particle beam RT has potential benefits for salvaging patients with locally recurrent head and neck cancer who previously were treated with high-dose RT. The unique physical characteristics of the Bragg peak of particle beams enables more precise dose localization to the recurrent foci, thereby reducing the toxicities to normal tissues that are heavily irradiated at the time of initial RT. In addition, the higher relative biological effectiveness (RBE) of a heavy ion such as carbon ion results in the more effective killing of cancer cells that are resistant to conventional photon irradiation.[8] The benefits of carbon-ion RT (CIRT) in the salvage treatment of patients with locally recurrent head and neck malignancies (non-NPC) have been reported by the Heidelberg Ion Therapy Center of Heidelberg University

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Hospital.[9] In addition, in our preliminary study of 75 patients with LR-NPC who were salvaged with intensity-modulated CIRT, we demonstrated a favorable 1-year OS rate of 98.1%.[10] The objective of the current study was to begin to bolster the existing literature by documenting the outcome of a large group of patients consecutively treated at the Shanghai Proton and Heavy Ion Center (SPHIC) using intensity-modulated CIRT with raster scanning technology.

MATERIALS AND METHODS

Patients

All patients were treated previously with definitive photon-based RT but developed locoregional disease recurrence. Patients with distant metastasis were excluded. A recurrence-free period of >6 months after the completion of the initial RT was required. Patients were treated either with the CIRT regimens of 1 of the 3 phase 1/2 clinical trials (ClinicalTrials.gov NCT02569788, ClinicalTrials.gov NCT02801487, or ClinicalTrials.gov NCT02795195) or the standardized treatment protocol if a trial was not available at the time of consultation or participation was rejected. Eligibility for a clinical trial or treatment protocol was confirmed at our institutional multidisciplinary tumor clinic. The current study was approved by the institutional review board of SPHIC with a waiver of the informed consent considering its retrospective nature, and was conducted in accordance with the ethical standards established by the 1964 Declaration of Helsinki and its later amendments.

Baseline evaluations consisted of a complete history and physical examination, nasopharyngoscopy, complete blood counts, serum electrolyte tests, hepatic and renal function tests, urinalysis, and electrocardiogram. Magnetic resonance imaging (MRI) with contrast of the head and neck was required for all patients to evaluate the extent of locoregional disease. If contraindicated, enhanced computed tomography (CT) could be used instead. Whole-body positron emission tomography/CT was recommended for all patients to rule out distant metastasis but could be replaced with CT of the thorax, ultrasound of the abdomen, and bone scan. Evaluation for potential neck dissection was required for all patients with neck lymphadenopathy. Neck lymph node resection usually is recommended for patients with disease recurrence in the neck; however, for patients for whom surgery is not feasible, neck adenopathy also can be managed by CIRT. Metastatic retropharyngeal lymph nodes were encompassed in the CIRT field. All patients were restaged according to the seventh or eighth edition of the American Joint Committee on Cancer staging classification for their recurrent disease diagnosed before or after January 1, 2018.

Carbon-Ion RT

The CIRT techniques were detailed previously.[10] Briefly, all patients were immobilized in the supine position with thermoplastic masks. CT simulation from the vertex to the inferior margin of the clavicular heads was performed at a 1.5-mm cut. Fusion of MRI performed at treatment position to planning CT was required for patients without contraindications. The gross tumor volume (GTV) included all disease noted on physical examination and/or imaging studies. The clinical target volume(s) were designed to include 5 mm beyond the GTV for microscopic extension (limited to ≥1 mm near critical organs). An additional margin measuring 3 mm to 6 mm was added to the clinical target volume to create the planning target volume to allow for setup errors and the uncertainty of particle beam dose distribution. Elective lymph node irradiation to uninvolved neck regions was not performed. Organs at risk (OARs) including the brainstem, spinal cord, temporal lobes, eyes and lens, optic nerves and chiasm, cochleae, parotid glands, and temporomandibular joints were delineated in all cases. The dose constraints of the OARs were established according to the tolerance dose (TD5/5) published by Emami et al or the experience from the National Institute of Radiological Sciences of Japan.[11,12] Recovery from the initial course of IMRT was set at 70% for all patients regardless of the time interval between the initial and salvage RT courses based on the radiobiological conclusions of Nieder et al.[13] Dose constraints for critical organs were detailed in Supporting Table S11.

The total dose and fraction scheme used for each individual patient are detailed in Table 1 and were dependent on the treatment and trial protocols used. CIRT planning was performed using the Siemens Syngo® treatment planning system (versions VC11 and 13). Two to 3 beams (2 opposed lateral beams with or without a vertex beam) typically were used. A typical treatment plan for a patient with LR-NPC without neck lymphadenopathy is shown in Figure 1.

All patients were evaluated weekly for toxicities. Weekly CT scans of the head and/or neck region were performed after week 2 of CIRT for all patients to ensure the consistency of the anatomy within the treatment field and the dose distribution.

TABLE 1. Dose and Fractionation Schemes Used For the CIRT of 206 Patients With LR-NPC

Protocol Type	Features	Dose and Fractionation	Status
Phase 1/2 clinical trial (Clinical Trials.gov identifier NCT02569788)	CIRT dose escalation without concurrent cisplatin	From 57.5 GyE at 2.5 GyE per daily fraction	Discontinued[a]; 9 patients in the current study were treated according to this protocol
Phase 1/2 clinical trial (Clinical Trials.gov identifier NCT02801487)	CIRT dose escalation with concurrent cisplatin	From 55 GyE at 2.5 GyE per daily fraction	Discontinued[a]; 6 patients in the current study were treated according to this protocol
Phase 1/2 clinical trial (Clinical Trials.gov identifier NCT02795195)	CIRT dose escalation then phase 2 study without concurrent chemotherapy	From 54 GyE at 3.0 GyE per daily fraction	Phase 1 was completed, and the MTD was 63 GyE; the patient accrual for the phase 2 study was completed; 51 patients in the current study were treated according to this protocol
SPHIC treatment protocol	Standardized treatment protocol for patients who decline trial participation or those for whom trial(s) were not available, including the pilot study conducted at the beginning of practice	60-69 GyE at 3.0 GyE per daily fraction; for the pilot study, 50-66 GyE at 2.0-3.0 GyE per daily fraction dependent on the recurrent T category (higher dose for earlier T classification disease) and OAR tolerance	A total of 140 patients in the current study were treated according to this protocol; the median CIRT dose was 63.0 GyE (range, 50.0-69.0 GyE), and a total of 105 patients (75.0%) received a dose ≥63 GyE; the median dose per fraction was 3.0 GyE (range, 2.0-3.0 GyE) and 123 patients (87.9%) were treated with a fraction size of 3.0 GyE; 81 (57.9%) patients and 33 patients (23.6%), respectively, received induction chemotherapy and concurrent chemotherapy

Abbreviations: CIRT, carbon-ion radiotherapy; GyE, gray equivalent; LR-NPC, locoregionally recurrent nasopharyngeal carcinoma; MTD, maximum tolerated dose; OAR, organs at risk; RT, radiotherapy; SPHIC, Shanghai Proton and Heavy Ion Center.
[a]Two phase 1/2 studies were discontinued due to slow accrual, although no severe acute or subacute toxicities were observed. Focus was given to the third phase 1/2 trial at a dose of 3.0 GyE per daily fraction without concurrent chemotherapy.

Chemotherapy

Platin-based neoadjuvant chemotherapy was recommended to all patients with locally advanced (recurrent stage III-IVB) LR-NPC. No particular regimen was required, but the most commonly used was cisplatin combined with docetaxel. Concurrent chemotherapy with cisplatin was prescribed at the discretion of the attending radiation oncologist, but generally was not recommended except for patients accrued to the phase 1/2 trial examining the safety and efficacy of chemotherapy used currently with CIRT (ClinicalTrials.gov identifier NCT02801487).[14] Among the 38 patients who received concurrent chemotherapy, 30 patients received cisplatin (at a dose of 25 mg/m^2 on days 1-3) every 3 weeks and 8 patients received cisplatin (at a dose of 40 mg/m^2 on day 1) weekly. Adjuvant chemotherapy was not recommended.

Follow-Up

According to the institutional follow-up protocol and individual trial protocols, patients were required to be followed by their primary radiation oncologist within 4 to 6 weeks after the completion of CIRT, every 3 months within the first 2 years, every 6 months in the subsequent 3 years, and annually thereafter. MRI scans of the head and neck were required at the time of each follow-up visit. Positron emission tomography/CT, CT of the thorax and/or abdomen, and/or ultrasound of the abdomen were optional and were ordered at the discretion of the radiation oncologist to rule out distant metastasis.

Data Analysis

OS was defined as the time from the diagnosis of disease recurrence to death. Local control, regional control, and distant control were defined as the times from the diagnosis of disease recurrence to local, regional, or distant failure, respectively. The treatment response was based on the findings of imaging studies using Response Evaluation Criteria in Solid Tumors (version 1.1).[15] Toxicities that occurred within 90 days after the initiation of CIRT were defined as acute toxicities and were measured using the Common Terminology Criteria for Adverse Events (version 4.03), whereas late toxicities were defined as those first observed 90 days after or those lasting for >90 days after the initiation of CIRT, and were graded according to the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria.[16] Mucosal necrosis was identified on MRI as low-intensity defects of the mucosa that could be surrounded by an enhanced rim. Because it is difficult to differentiate radiation-induced necrosis from that caused by tumor progression solely on imaging studies, newly developed and/or enlarged necrosis within the tumor bed was considered as CIRT induced only when no concurrent tumor progression was observed.

Statistical Analysis

OS, local control, regional control, and distant control rates were calculated using the Kaplan-Meier method. Univariable and multivariable analyses regarding OS and local control were conducted using the Cox regression

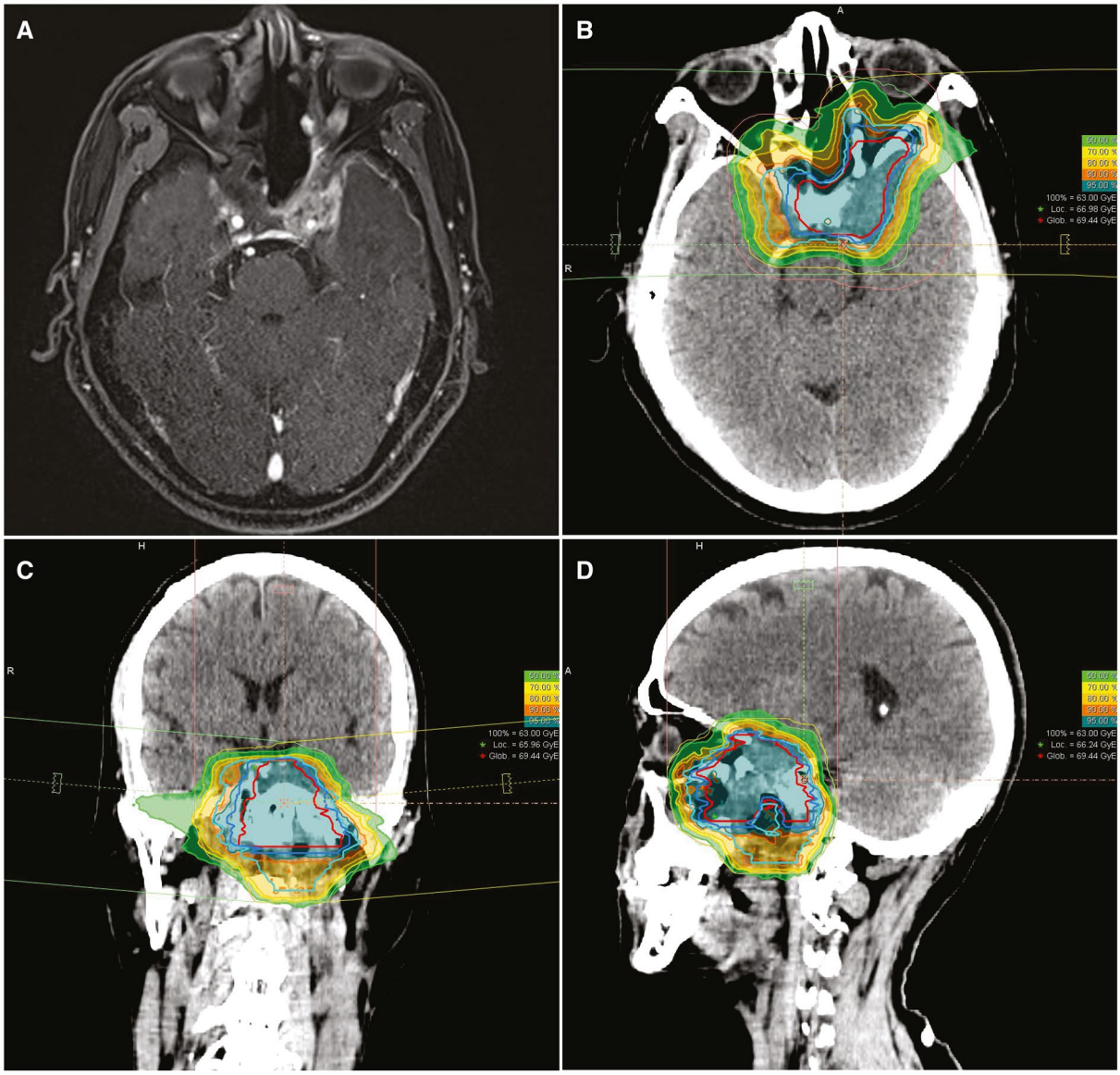

FIGURE 1. A typical carbon-ion radiotherapy (CIRT) treatment plan with 3 fields. This patient with locally advanced, locoregionally recurrent nasopharyngeal carcinoma (T4N0M0 disease) received CIRT of 63 gray equivalent in 21 fractions.

model. Baseline characteristics and treatment information were included in the univariable and multivariable analyses with the exception of the RT technique used for primary treatment because only 8 patients in the current study cohort previously were irradiated using a technique other than IMRT. Because various fraction sizes were used, CIRT doses were converted to the biological equivalent dose (BED), and the BED was included in the analyses instead of dose to the GTV and fractionation. The chi-square test or Wilcoxon test was used to examine the relationships between baseline characteristics and the occurrence of a massive hemorrhage subsequent to mucosal necrosis. P values $<.05$ were considered to be statistically significant. Statistical analyses were performed using R statistical software (version 3.5.1).

RESULTS

Study Population

Between May 2015 and June 2019, a total of 209 patients with LR-NPC underwent consultation and were treated with CIRT at SPHIC. One patient who had distant metastasis at baseline was excluded, as were 2 additional patients who prematurely discontinued their treatment.

Therefore, a total of 206 patients were included in the current analysis. The characteristics of the entire cohort and their treatment are detailed in Table 2.

Disease Control and Survival

At a median follow-up of 22.8 months (range, 2.0-74.6 months), a total of 38 patients had died. Among those patients, 22 patients (57.9%) died of tumor progression, 10 patients (26.3%) died of massive hemorrhage subsequent to mucosal necrosis, and 4 patients (10.5%) died of conditions unrelated to LR-NPC or CIRT-induced toxicities. The cause of death was not obtained for 2 additional patients (5.3%). Sixty-nine patients, 21 patients, and 11 patients, respectively, developed local disease progression, regional disease progression, and distant metastasis, respectively. The 2-year OS, local control, regional control, and distant control rates were 83.7% (95% confident interval [CI], 78.0%-89.7%), 58.0% (95% CI, 50.0%-67.2%), 87.3% (95% CI, 81.7%-93.3%), and 94.7% (95% CI, 91.1%-98.4%), respectively (Fig. 2).

Adverse Effects

Salvage CIRT for patients with LR-NPC after RT to a definitive dose appeared to be well tolerated. No patient developed ≥grade 3 radiation-induced adverse effects within 90 days after the initiation of CIRT. The most observed acute side effects found to be associated with salvage CIRT were mild (grade 1/2) skin reaction (0.97%) and mucosa erythema (16.50%). The incidences of late toxicities are detailed in Table 3. Massive hemorrhage subsequent to mucosal necrosis occurred in 16 patients (7.77%), and 10 patients (4.85%) died. The median time to the development of a massive hemorrhage was 7.0 months (range, 2.8-21.8 months) after the completion of CIRT. Among the baseline characteristics, a larger tumor volume was found to be significantly associated with an increased incidence of a massive hemorrhage ($P = .010$). Concurrent chemotherapy was not associated with increased acute and/or late toxicities.

Prognostic Analysis

On univariable analyses, older age (hazard ratio [HR], 2.04; 95% CI, 1.03-4.06 [$P = .041$]), advanced stage of disease at the time of recurrence (HR, 2.61; 95% CI, 1.15-5.94 [$P = .022$]), and larger GTV (HR, 2.51; 95% CI, 1.28-4.93 [$P = .007$]) were found to be significantly associated with worse OS (Table 4). Larger GTV (HR, 1.71; 95% CI, 1.06-2.75 [$P = .027$]) and a

TABLE 2. Characteristics at Baseline and Treatment Modalities (N = 206)

Characteristics	No. of Patients
Age, y	
Median (range)	49 (17-73)
<60	170 (82.52%)
≥60	36 (17.48%)
Sex	
Female	53 (25.73%)
Male	153 (74.27%)
DFI, mo	
Median (range)	28.6 (4.4-393.5)
<12	22 (10.68%)
≥12	184 (89.32%)
Initial RT technique	
IMRT + CIRT[a]	1 (0.49%)
IMRT	194 (94.17%)
Non-IMRT	8 (3.88%)
Unknown	3 (1.46%)
Histological classification[b]	
Nonkeratinizing undifferentiated carcinoma	148 (71.85%)
Nonkeratinizing differentiated carcinoma	26 (12.62%)
Squamous cell carcinoma, NOS	32 (15.53%)
Recurrent tumor classification	
T0	20 (9.71%)
T1	24 (11.65%)
T2	26 (12.62%)
T3	60 (29.13%)
T4	76 (36.89%)
Recurrent lymph node classification	
N0	140 (67.96%)
N1	53 (25.73%)
N2	8 (3.88%)
N3	5 (2.43%)
Recurrent AJCC disease stage	
I	17 (8.25%)
II	50 (24.27%)
III	60 (29.13%)
IV[c]	79 (38.35%)
Median GTV (range), mL	22.46 (1.72-201.49)
Baseline necrosis	
Absent	153 (74.27%)
Present	53 (25.73%)
Salvage CIRT dose to GTV, GyE	
Median (range)	63 (50-69)
<63	63 (30.58%)
≥63	143 (69.42%)
Fractionation, GyE	
Median (range)	3 (2-3)
<3	31 (15.05%)
3	175 (84.95%)
Median BED, GyE	81.9 (60-89.7)
Chemotherapy	
Chemotherapy prior to CIRT	126 (61.17%)
Chemotherapy concurrent with CIRT	38 (18.45%)

Abbreviations: AJCC, American Joint Committee on Cancer; BED, biological equivalent dose; CIRT, carbon-ion radiotherapy; DFI, disease-free interval; GTV, gross tumor volume; GyE, gray equivalent; IMRT, intensity-modulated radiotherapy; NOS, not otherwise specified; RT, radiotherapy.

[a]One patient previously was treated with a combination of IMRT and CIRT. This patient underwent IMRT of 56 Gy and 50.4 Gy, respectively, to a high-risk area and low-risk area in 28 fractions, followed by a CIRT boost of 15 GyE in 5 fractions to the GTV.

[b]Of the 206 patients, 82 patients were diagnosed with disease recurrence on imaging study only. For those patients, the histology of the primary disease was used.

[c]No patient was found to have distant metastasis.

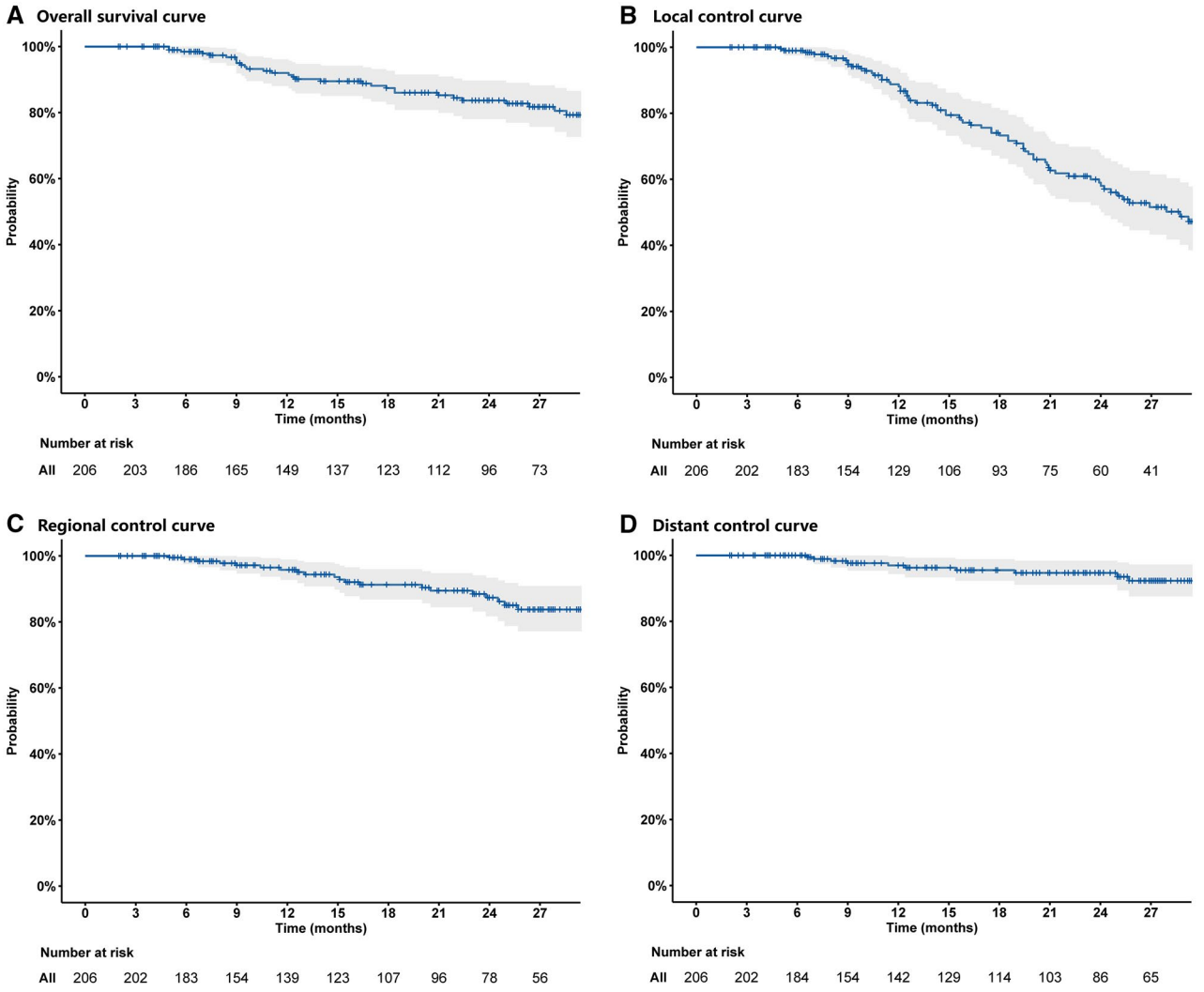

FIGURE 2. Curves of (A) overall survival (OS), (B) local control, (C) regional control, and (D) distant control among patients in the current study cohort. The corresponding 2-year OS, local control, regional control, and distant control rates were 83.7% (95% confidence interval [CI], 78.0%-89.7%), 58.0% (95% CI, 50.0%-67.2%), 87.3% (95% CI, 81.7%-93.3%), and 94.7% (95% CI, 91.1%-98.4%), respectively.

TABLE 3. Late Toxicities Related to CIRT (N = 206)[a]

Characteristics	Grade 1/2	≥Grade 3
Nasopharyngeal necrosis[b]	0	33 (16.02%)[c]
Temporal lobe necrosis	24 (11.65%)	2 (0.97%)
Cranial neuropathy	21 (10.19%)	1 (0.49%)
Hearing impairment	12 (5.83%)	3 (1.46%)
Xerostomia	15 (7.28%)	1 (0.49%)

Abbreviation: CIRT, carbon-ion radiotherapy.
[a]Toxicities were graded using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria.
[b]Some of the patients had necrosis within the tumor bed. For those patients, nasopharyngeal necrosis was counted only if they did not have concurrent local disease progression.
[c]Sixteen patients had subsequent massive hemorrhage, and 10 patients died.

lower BED (HR, 0.56; 95% CI, 0.35-0.90 [$P = .017$]) were found to be significantly associated with worse local control. On multivariable analyses, age (HR, 2.46; 95% CI, 1.17-5.16 [$P = .017$]) was significantly related to OS, whereas GTV (HR, 1.87; 95% CI, 1.00-3.48 [$P = .049$]) and BED (HR, 0.56; 95% CI, 0.33-0.94 [$P = .029$]) were found to be related to local control (Table 5, Fig. 3). In addition, a trend toward worse OS was observed on univariable analysis (HR, 1.85; 95% CI, 0.91-3.78 [$P = .09$]) and multivariable analysis (HR, 2.05; 95% CI, 0.94-4.48 [$P = .072$]) for patients who had mucosal necrosis at baseline.

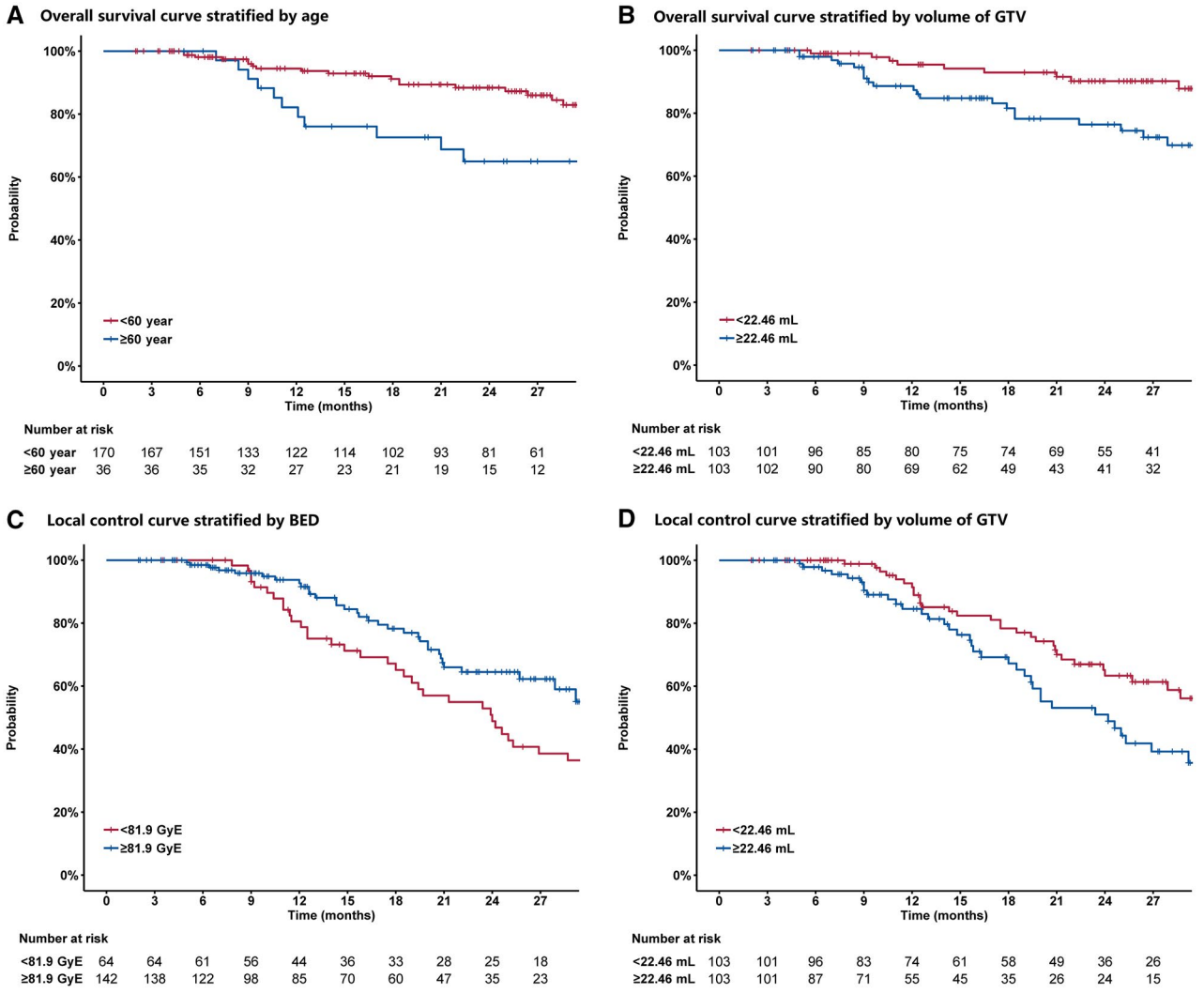

FIGURE 3. Overall survival (OS) curves stratified by (A) age (≥60 years vs <60 years) and (B) gross tumor volume (GTV) (≥22.46 mL vs <22.46 mL; median GTV, 22.46 mL). Local control curves stratified by (C) biological equivalent dose (BED) (≥81.9 gray equivalent [GyE] vs <81.9 GyE; median BED, 81.9 GyE) and (D) GTV (≥22.46 mL vs <22.46 mL). On multivariable analyses, age ≥60 years (hazard ratio [HR], 2.46; 95% CI, 1.17-5.16 [*P* = .017]) was related to significantly worse OS, and a trend toward worse OS was observed for patients with a tumor volume of ≥22.46 mL (HR, 2.24; 95% CI, 0.97-5.17 [*P* = .060]) whereas a BED <81.9 GyE (HR, 0.56; 95% CI, 0.33-0.94 [*P* = .029]) and a tumor volume of ≥22.46 mL (HR, 1.87; 95% CI, 1.00-3.48 [*P* = .049]) were associated with significantly inferior local control.

DISCUSSION

In the current analysis of 206 patients with LR-NPC who failed previous definitive RT, we found that salvage CIRT achieved 2-year OS, local control, regional control, and distant control rates of 83.7%, 58.0%, 87.3%, and 94.7%, respectively. More important, salvage CIRT appeared to be well tolerated. No patient developed ≥grade 3 adverse events within 90 days after the initiation of CIRT, and <20% of patients experienced severe (ie, ≥ grade 3) late toxicities, including 16% with mucosal necrosis. Such outcomes appeared to be substantially improved from the historical results after salvage IMRT. In addition, the results of multivariable analysis demonstrated that age was significantly associated with OS, whereas the volume of the recurrent disease foci and the BED were associated with local control.

LR-NPC poses a substantial challenge to oncologists. Surgical resection and stereotactic radiosurgery are suitable only for a limited percentage of patients with a small disease volume.[1] Systemic treatment may postpone disease progression but does not provide the potential for long-term disease control or cure, and therefore was reserved only for those patients who were not amenable to definitive local treatment. Photon-based IMRT

TABLE 4. Univariable Analysis of OS and Local Control

Characteristics	OS		Local Control	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥60 y vs <60 y)	2.04 (1.03-4.06)	.041	0.85 (0.45-1.63)	.63
Sex (male vs female)	0.80 (0.39-1.61)	.53	0.88 (0.52-1.48)	.63
DFI (≥1 y vs <1 y)	0.89 (0.35-2.27)	.80	0.85 (0.39-1.85)	.68
Recurrent AJCC disease stage (stage III/IV vs I/II)	2.61 (1.15-5.94)	.022	1.52 (0.91-2.55)	.11
GTV (≥22.46 mL vs <22.46 mL)[a]	2.51 (1.28-4.93)	.007	1.71 (1.06-2.75)	.027
Baseline necrosis (present vs absent)	1.85 (0.91-3.78)	.090	1.20 (0.67-2.15)	.54
BED (≥81.9 GyE vs <81.9 GyE)[b]	0.63 (0.31-1.28)	.20	0.56 (0.35-0.90)	.017
Chemotherapy prior to CIRT (with vs without)	1.44 (0.73-2.86)	.30	0.89 (0.55-1.44)	.64
Chemotherapy concurrent with CIRT (with vs without)	0.82 (0.34-1.97)	.65	0.95 (0.52-1.75)	.88

Abbreviations: AJCC, American Joint Committee on Cancer; BED, biological equivalent dose; CI, confidence interval; CIRT, carbon-ion radiotherapy; DFI, disease-free interval; GTV, gross tumor volume; GyE, gray equivalent; HR, hazard ratio; OS, overall survival.
[a]The median GTV was 22.46 mL.
[b]The median BED was 81.9 GyE.

TABLE 5. Multivariable Analysis of OS and Local Control

Characteristics	OS		Local Control	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥60 y vs <60 y)	2.46 (1.17-5.16)	.017	0.81 (0.41-1.61)	.55
Sex (male vs female)	0.61 (0.29-1.28)	.19	0.89 (0.52-1.53)	.67
DFI (≥1 y vs <1 y)	0.77 (0.29-2.05)	.60	0.83 (0.37-1.84)	.64
Recurrent AJCC disease stage (stage III/IV vs I/II)	1.46 (0.53-4.03)	.46	1.23 (0.65-2.34)	.53
GTV (≥22.46 mL vs <22.46 mL)[a]	2.24 (0.97-5.17)	.060	1.87 (1.00-3.48)	.049
Baseline necrosis (present vs absent)	2.05 (0.94-4.48)	.072	1.32 (0.70-2.47)	.39
BED (≥81.9 GyE vs <81.9 GyE)[b]	0.61 (0.29-1.30)	.20	0.56 (0.33-0.94)	.029
Chemotherapy prior to CIRT (with vs without)	1.08 (0.51-2.31)	.84	0.57 (0.32-1.02)	.060
Chemotherapy concurrent with CIRT (with vs without)	0.62 (0.25-1.55)	.31	0.87 (0.45-1.67)	.68

Abbreviations: AJCC, American Joint Committee on Cancer; BED, biological equivalent dose; CI, confidence interval; CIRT, carbon-ion radiotherapy; DFI, disease-free interval; GTV, gross (macroscopic) tumor volume; GyE, gray equivalent; HR, hazard ratio; OS, overall survival.
[a]The median GTV was 22.46 mL.
[b]The median BED was 81.9 GyE.

remains the most commonly used treatment, especially for patients with locally advanced disease. However, published experiences in endemic regions have demonstrated dismal outcomes after reirradiation using IMRT, with a 2-year OS rate ranging from approximately 60% to 70%.[6,7,17] Radiation-induced toxicities were the most important cause of mortality, and accounted for >50% of patient deaths. In a large cohort of 239 patients with LR-NPC, the researchers found that IMRT yielded a 5-year OS rate of 44.9%.[6] Meanwhile, radiation-induced severe late toxicities were common, including 97 patients (40.6%) with severe inflammation or necrosis of the nasopharynx. Among the 120 patients in the study who were reported to have died, 83 (69.2%) died of radiation-induced toxicities. Similar results were observed in a more recent study of 184 patients with LR-NPC who were treated with IMRT.[17] After a median follow-up of 32 months, the OS rates at 3 years and 5 years were 46.0% and 28.8%, respectively, whereas mucosal necrosis was observed in 56 patients (44 of whom died of a subsequent massive hemorrhage). In another cohort of 77 patients with LR-NPC who failed previous IMRT, the authors demonstrated that salvage IMRT yielded OS rates of 68% and 51.5%, respectively, at 2 years and 3 years.[7] Severe toxicities were observed in 50 patients (64.9%), and were a major cause of death, accounting for greater than one-half of the deaths. Among the toxicities, mucosal necrosis was reported to occur in 31 patients (40.3%). Clearly, more effective and safe RT is needed for managing patients with LR-NPC.

Particle beam RT such as proton beam or CIRT permits a sharp dose distribution, allowing for OARs adjacent to the disease foci to be spared, a feature that is of particular importance within the setting of

reirradiation in patients with LR-NPC. Several dosimetry studies have confirmed the superior dose distributions of particle beam RT for reirradiation in patients with LR-NPC.[18,19] However, clinical experiences using proton therapy for the treatment of patients with LR-NPC demonstrated perplexing results. In a retrospective analysis of 92 patients (76 of whom had received 1 prior RT course and 16 of whom had received ≥2 courses) with recurrent head and neck cancer, a medical condition that is comparable to LR-NPC, Romesser et al demonstrated that the toxicity profile of proton therapy was acceptable even for those patients who already had received >1 course of RT; however, the 1-year incidence of locoregional failure and the OS rate were 25.1% and 65.2%, respectively.[20] In an early series of 16 patients with LR-NPC (75% of whom had locally advanced disease) who were treated at Loma Linda University Medical Center, proton therapy yielded a 2-year OS rate of 50%.[21] In another recent series of 17 patients with LR-NPC who were treated with proton therapy, the authors showed the 18-month OS and local control rates to be 54.4% and 66.6%, respectively, after a median follow-up of 10 months.[22]

In addition to its dosimetric advantages, accelerated, heavy charged particle beam therapy has a substantially higher RBE. For example, the RBE is 3 to 5 for CIRT compared with photon and proton RT depending on the tissue type and endpoint of the study. It has been suggested that up to 70% of the CIRT-induced damage occurs in the form of direct DNA double-strand breaks, which are more difficult to repair.[23] Therefore, improved clinical outcomes could be expected from heavy charged particle therapy, especially for patients with radioresistant cancers, including recurrent tumors, who have failed previous courses of RT. In an early series of 16 patients with locally advanced, recurrent NPC, Feehan et al demonstrated that helium or neon could provide a 3-year OS rate of 59% despite the lack of imaging guidance.[24] The safety and effectiveness of CIRT as reirradiation for patients with recurrent tumors in the skull base initially was demonstrated by Combs et al.[9] In this study, 18 patients received CIRT (2 received stereotactic proton therapy with a carbon-ion boost). The results demonstrated a satisfactory OS rate of 86% at 2 years. And our preliminary results of the first 75 patients with LR-NPC indicated that salvage CIRT appeared to provide a superior OS and toxicity profile compared with IMRT.[10]

In the current study, tumor volume was demonstrated to be an independent prognostic factor for local control. In addition, a trend toward worse OS also was observed for patients with a larger tumor volume. A similar result previously was reported by Xiao et al within the setting of IMRT as reirradiation for patients with LR-NPC.[25] Therefore, tumor volume may be an important factor to consider when choosing the appropriate candidates for reirradiation using CIRT.

To overcome the variety of dose and fractionation combinations used in the current study cohort, the BED was calculated and used as a covariable in regression analyses. The results demonstrated that a BED of ≥81.9 gray equivalent (GyE) was associated with significantly improved local control, but not OS. It could be in part because a high dose of reirradiation may be related to an increased risk of developing severe toxicities such as mucosal necrosis and subsequent hemorrhage, thereby reducing the OS. Therefore, during salvage CIRT, a high dose should be used only among carefully selected patients (such as those with smaller tumor volume and no obvious baseline necrosis).

Mucosal necrosis is one of the most challenging toxicities for patients with LR-NPC who undergo reirradiation. It can significantly reduce patients' quality of life and cause subsequent fatal hemorrhage. Previous studies regarding photon-based IMRT have demonstrated that approximately 40% of patients may develop mucosal necrosis.[6,7] Subsequent fatal hemorrhage was reported to occur in >20% of patients.[7] Although the incidences of mucosal necrosis (16.02%) and subsequent fatal hemorrhage (4.85%) were reduced substantially by CIRT, they still remain a serious concern. At SPHIC, debridement surgery is recommended when obvious mucosal necrosis is observed. In addition, if a patient was considered to be at high risk of developing subsequent hemorrhage (such as exposure or deformation of the carotid artery detected on MRI), we would ask the patient to consult a physician for endovascular therapy. It is interesting to note that the median time to developing a massive hemorrhage after CIRT was 7 months. Therefore, the results of the current study were able to provide a relatively accurate evaluation of massive hemorrhage related to CIRT, although the follow-up of the cohort was relatively short.

To the best of our knowledge, the current study is the largest series to date to document the results of CIRT as reirradiation for patients with recurrent cancer. Nevertheless, several pitfalls need to be addressed. The current study was retrospective in nature and thus was subject to the corresponding limitations. However, all patients were treated according to 1 of the 3 phase 1/2 trials or our prospectively designed institutional protocol, therefore reducing the introduced bias. The

usefulness of induction and concurrent chemotherapy may not have been addressed in the current study. Some of the patients were not deemed to be candidates for definitive RT before they were referred to SPHIC and had already received various cycles of chemotherapy as palliative treatment. By definition, those treatments could not be regarded strictly as induction chemotherapy. While concurrent chemotherapy was not recommended for patients who were not accrued to the phase 1/2 trial. Prospective trials therefore are necessary to examine the role of chemotherapy within the setting of CIRT for patients with LR-NPC.

Conclusions

Generally, salvage treatment using CIRT appears to be efficacious for patients with LR-NPC, and its toxicities are acceptable. With a median follow-up of 22.8 months, the 2-year OS rate in the current study was 83.7%. Moderate to severe acute toxicities were rare, whereas the probability of late serious adverse events remained infrequent compared with the use of IMRT. Nevertheless, mucosal necrosis was observed in approximately 16% of the patients and caused 10 deaths due to subsequent fatal hemorrhages. Although CIRT could provide an improved outcome, reirradiation using CIRT should be administered with caution for patients with extensive tumor volume and/or massive necrosis (especially when the carotid arteries are involved). Because randomized trials comparing CIRT and IMRT for patients with LR-NPC are difficult if not impossible because of the limited availability of the treatment facilities and the imbalanced accrual of patients caused by the cost and reimbursement of particle beam RT, propensity score-matched analysis may serve as a reliable method for accurate comparison.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jiyi Hu: Conceptualization, data curation, formal analysis, methodology, validation, visualization, funding acquisition, writing–original draft, and writing–review and editing. **Qingting Huang:** Data curation, formal analysis, validation, writing–original draft, and writing–review and editing. **Jing Gao:** Data curation, validation, writing–original draft, and writing–review and editing. **Xiyin Guan:** Data curation, validation, writing–original draft, and writing–review and editing. **Weixu Hu:** Data curation, validation, writing–original draft, and writing–review and editing. **Jing Yang:** Data curation, validation, writing–original draft, and writing–review and editing. **Xianxin Qiu:** Data curation, validation, writing–original draft, and writing–review and editing. **Mingyuan Chen:** Resources, writing–original draft, and writing–review and editing. **Lin Kong:** Conceptualization, formal analysis, methodology, validation, resources, funding acquisition, supervision, writing–original draft, and writing–review and editing. **Jiade J. Lu:** Conceptualization, formal analysis, methodology, validation, resources, funding acquisition, supervision, writing–original draft, and writing–review and editing.

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