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ORIGINAL ARTICLE

LINAC-based Fractionated Stereotactic Radiotherapy for Residual and Recurrent Nasopharyngeal Carcinoma in the Era of Intensity-modulated Radiotherapy: A 10-year Experience

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ABSTRACT

Introduction: *We reviewed the use of frameless linear accelerator–based fractionated stereotactic radiotherapy (FSRT) in a single centre as salvage treatment for patients with nasopharyngeal carcinoma with local failure.*

Methods: *We retrospectively reviewed the data of all patients with residual or recurrent nasopharyngeal carcinoma who had undergone salvage therapy with FSRT at our institution between 2008 and 2017. Survival data were analysed by the Kaplan-Meier method. Univariate analyses for survival outcomes were performed using the Cox proportional hazards model. Severe late radiation toxicities were assessed.*

Results: *Of the 49 patients included, 44 (90%) had previously received intensity-modulated radiotherapy as primary treatment. The median FSRT dose was 18 Gy in three fractions for residual disease, and 48 Gy in six fractions for recurrent disease. Median follow-up was 41.1 months. The 3-year local control rate, progression-free survival (PFS), disease-specific survival, and overall survival (OS) for patients with residual disease (n = 34) were 78.9%, 66.2%, 82.2%, and 74.0%, respectively. Those for patients with recurrent disease (n = 15) were 68.2%, 40.0%, 58.7%, and 46.7%, respectively. Using FSRT, a gross tumour volume of ≤16 mL of residual disease was associated with longer PFS and OS. N3 nodal staging status was associated with poorer PFS in the residual disease group. Severe late complications occurred in 12 patients (24%), including one patient from the residual disease group and four patients from the recurrent disease group with fatal haemorrhage (10%).*

Conclusion: *Using this less-invasive and resource-friendly technique, the clinical outcomes from our centre were comparable to those in the literature.*

Key Words: *Dose fractionation, radiation; Nasopharyngeal carcinoma; Neoplasm, residual; Salvage treatment*

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中文摘要

調強放療年代的殘存及復發性鼻咽癌的直線加速器分段立體定向放射治療：10年經驗回顧

劉芷珊、陳瓏、余洛汶、黎詠宇、袁錦堂、鄭志堅

引言：回顧無框架式直線加速器分段立體定向放射治療（FSRT）在一所本地醫院作為鼻咽癌局部失敗挽救性治療的療效和安全性。

方法：回顧2008年至2017年在本院接受FSRT治療的殘存及復發性鼻咽癌患者，評估腫瘤反應和放療毒性。使用Kaplan-Meier法計算生存數據，以Cox比例風險回歸模型分析存活率風險因子。

結果：共納入49名患者，當中44名（90%）接受調強放療作為首次治療手段。殘存性鼻咽癌（34名）FSRT中位劑量為18Gy/3次，復發性鼻咽癌中位劑量為48Gy/6次。中位隨訪期為41.1個月。殘存性鼻咽癌（15名）3年局部控制率為78.9%，無惡化存活率為66.2%，無瘤存活率為82.2%，總存活率為74%。復發性鼻咽癌3年局部控制率為68.2%，無惡化存活率為40%，無瘤存活率為58.7%，總存活率為46.7%。在殘存性鼻咽癌患者中，腫瘤體積少於16 mL與較長無惡化存活期和總存活率期有關聯，而N3則與較短無惡化存活期有關聯。12名病人（24%）出現嚴重後期併發症，當中包括一名殘存性鼻咽癌患者和四名復發性鼻咽癌患者出現致命性出血（10%）。

結論：作為相對低入侵性及節省資源的放射治療方法，本研究患者的治療效果和文獻記載相若。

INTRODUCTION

Nasopharyngeal cancer (NPC) is common in Southeast Asia, especially Southern China. Despite a continued decreasing trend, the latest reported incidence in Hong Kong is 12 per 100 000, ranking tenth among the commonest cancers in the region.[1]

Intensity-modulated radiotherapy (IMRT) allows remarkable improvement in dose conformity compared with two-dimensional or three-dimensional conformal radiotherapy (RT), and IMRT use is associated with better survival outcomes and less treatment toxicity in NPC.[2] In modern series using IMRT, the reported local failure rate is 5% to 15% for earlier stages, but is much higher, 15% to 45%, for T4 disease.[3,4] The Hong Kong Nasopharyngeal Cancer Study Group (HKNPCSG) 1301 study evaluated more than 3000 patients treated with primary IMRT. Despite a low overall local recurrence rate of 3.9%, the 8-year actuarial local failure-free survival was only 71.6% for T4 disease, in contrast to the satisfactory outcomes of T1 to T3 disease (87%-92%).[5]

Management of local failure requires consideration of multiple factors, including location and extent of disease, availability of modality and expertise, as well as the patients' preferences and co-morbidities. An operative approach with nasopharyngectomy has been reported to offer favourable local control, but is often challenging due to the complex anatomy. A high level of surgical expertise is required, and such surgery is only feasible for patients with lower rT stages (rT1 to limited rT3).[6-8] It may also be less favoured for patients with significant concerns to operative risks and cosmetic result especially for open surgery. Nonoperative approaches include reirradiation with IMRT, stereotactic radiotherapy (single or multiple fractions), brachytherapy (intracavitary or interstitial), and photodynamic therapy, with the latter two only for T1 to early T2 lesions. Chemotherapy may be added as a component of salvage treatment but should not be used alone if long-term control is pursued.[6-8]

Stereotactic single-fraction radiotherapy, also known as stereotactic radiosurgery (SRS), was first used as a treatment option for recurrent NPC in the late 1990s. However, the use of stereotactic frames with neurosurgery expertise was almost always required, which caused logistic challenges in practice, and the frames themselves were uncomfortable. Fractionated stereotactic radiotherapy (FSRT) adopts the concept of precision in SRS but delivers the dose in multiple fractions, resulting in a better therapeutic ratio based on radiobiology principles. A matched cohort analysis

showed better 3-year local failure-free survival rates with FSRT than with single-fraction SRS, especially for recurrent and non-T1 disease.[9] The concerns of FSRT being more resource-intense and the issue of interfractional reproducibility have been tackled by advancements in treatment delivery speed and in stereotactic systems. LINAC-based frameless stereotactic systems are now commercially available, allowing FSRT to be delivered in a less-invasive and resource-friendly manner.

METHODS

Patients

The data of all patients with NPC local failure treated with reirradiation by FSRT in our institution between 2008 and 2017 were retrospectively reviewed. Patients with residual disease (residual tumour or relapse within 6 months of primary RT completion) and recurrent disease (relapse beyond 6 months of primary RT completion) were analysed.

Primary Treatment Methods

The primary RT treatment was a course of high-dose IMRT, delivering 70 Gy to the gross tumour, lymphadenopathy and nasopharynx, 60 Gy to the high-risk subclinical sites and lymphatic regions, and 54 Gy to the low-risk lymphatic regions using simultaneous integrated boosts, one fraction per day on weekdays to total 33 to 35 fractions. Concurrent chemotherapy was administered to patients with stage III-IV and T2N1 disease (as an option for high-risk stage II).

Assessment of Residual or Recurrent Disease

For the residual disease group, all patients had completed radical RT as the primary treatment of NPC. Their tumour response was assessed by two fibreoptic nasopharyngoscopy sessions performed 8 and 10 weeks after completion of RT. A systematic six-site (bilateral roofs, lateral walls, and posterior walls) mapping biopsy of the nasopharynx was performed during each session, and remission was defined as two consecutive negative biopsies at each site. A positive biopsy at any one site in any of these two sessions warranted an additional session 12 weeks after RT. If the repeated biopsy was positive, the patient was considered to harbour persistent residual disease and salvage treatment (FSRT) was initiated, accounting for the residual disease group in this study.[10]

All patients considered free from persistent disease were followed up routinely with clinic visits and physical examinations. Investigations, such as fibreoptic nasopharyngoscopy and magnetic resonance imaging (MRI) were arranged on symptom presentation or abnormal physical findings. In the recurrent disease group, systemic re-staging was mandatory, with most patients undergoing positron-emission tomography and computed tomography (CT) scan to allow planning of FSRT.

Fractionated Stereotactic Radiotherapy Technique, Planning and Treatment Delivery

FSRT was performed using an Eclipse IMRS Planning System (Varian Medical Systems; Palo Alto [CA], United States), capable of delivering both cone and multileaf collimation–based IMRT by the Varian Clinac® iX linear accelerators.

Gross tumour volume (GTV) was contoured on the CT images using all available imaging data gathered by CT, MRI and positron-emission tomography/CT, as well as by endoscopic mapping. The planning target volume was generated by adding a 2-to-3-mm margin to the GTV. No elective reirradiation of regional lymph nodes was performed. Planning organ-at-risk (OAR) volumes were routinely contoured for critical neurological structures, including the brainstem, optic chiasm, optic nerves, and spinal cord by adding 3-mm margins to the optic chiasm, optic nerves and brainstem, and 5-mm margins to the spinal cord. In cases where the high-dose region was in close proximity to these OARs, smaller planning OAR volume margins (1-2 mm) would be used, where stringent image-guided treatment verification would be practised. The patients were informed of the relatively higher risk. Two treatment fractions per week, with an interfractional interval of at least 24 hours, were administered.

Different total doses and fractionations of FSRT were chosen based on the type of relapse (with residual disease considered more radiosensitive than recurrent disease), tumour extent, cumulative radiation dose for critical structures, and time interval from previous RT. For patients whose time interval between two RT courses was >1 year, a 33% to 50% dose tolerance recovery of central nervous system structures from the initial treatment course was assumed.[11] No patient received a cumulative lifetime biologically equivalent dose in 2-Gy fractions (EQD2) of >60 Gy to the brainstem[12] or optic chiasm, or 50 Gy to the spinal cord.[13]

Follow-up

After FSRT, tumour response was assessed by nasopharyngoscopy (with biopsy) and MRI. Regular

follow-up included clinical examination and toxicity assessment. Further imaging or endoscopy was arranged if clinically indicated.

Data Collection and Statistical Analyses

The cut-off date for data collection was 15 August 2018. The duration of follow-up was calculated from the date of completion of reirradiation to either the day of death or the day of the last follow-up.

The data were analysed to determine the pathological complete response rate to FSRT, local control rate, progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS).

Actuarial rates were calculated using the Kaplan-Meier method, and differences were compared using the log-rank tests. Univariate analyses using the Cox proportional hazards regression model were utilised to test the significance of different prognostic factors. Patient factors (age, sex, histological type, relapse-free interval for recurrent disease, time from pathological diagnosis of local failure to completion of treatment), tumour factors (initial T and N stage, recurrent T and N stage, FSRT GTV), and treatment factors (cumulative concurrent cisplatin dose, dose of FSRT [biologically effective dose with $\alpha/\beta = 10$ Gy; BED_{10}]) were included in univariate analyses. Time-dependent receiver operating characteristic analysis was used to determine the cut-off values of FSRT GTV in predicting survival outcome.

All analyses were performed using SPSS (Windows version 16.0; SPSS Inc, Chicago [IL], United States) and R (Version 3.5.1; www.r-project.org). The criterion for statistical significance was set at $p < 0.05$.

RESULTS

Patient Characteristics

All 49 patients with NPC local failure treated with reirradiation by FSRT in our institution were retrospectively reviewed. The median follow-up for the entire cohort was 41.1 (range, 3.7-118.1) months. Among them, 34 had residual disease and 15 had recurrent disease.

Overall, most tumours (>90%) were of the undifferentiated subtype (World Health Organization type III). For the residual tumour group, more than half of the patients had had locally advanced (T3/4) tumours at presentation. All patients had salvage FSRT completed within 6 months after residual disease was confirmed. In the recurrent disease group, most tumours were rT3 (53.3%). Five patients with recurrent disease had concomitant nodal recurrences (all N1-2); two were in the retropharyngeal region, which were treated with the same course of FSRT; three were in the cervical region and had undergone radical neck dissection. The median time from completion of primary treatment to recurrence was 21.5 months (range, 7.2-182.3 months). Before FSRT, 14 of 15 patients had had histological proof of recurrent carcinoma, except for one with an inaccessible site (retropharyngeal region), and the diagnosis was made by imaging. Detailed patient characteristics are shown in Table 1.

During the primary treatment course, 53% of patients received concurrent chemotherapy (mostly cisplatin-

Table 1. Patient and disease characteristics according to type of local relapse.*

	Residual disease (n = 34)	Recurrent disease (n = 15)
Sex		
Male	28 (82.4%)	10 (66.7%)
Female	6 (17.6%)	5 (33.3%)
Age at presentation (years)	55.5 (33-84)	49 (29-72)
WHO histologic type		
I	1 (2.9%)	0
II	2 (5.9%)	0
III	31 (91.2%)	15 (100%)
Primary T stage†		
T1	5 (14.7%)	1 (6.7%)
T2	7 (20.6%)	8 (53.3%)
T3	18 (52.9%)	5 (33.3%)
T4	4 (11.8%)	1 (6.7%)
Primary N stage†		
N0	11 (32.4%)	5 (33.3%)
N1	16 (47.1%)	3 (20%)
N2	5 (14.7%)	6 (40%)
N3	2 (5.9%)	1 (6.7%)
Recurrent T stage†‡		
rT1		6 (40%)
rT2		1 (6.7%)
rT3		8 (53.3%)
rT4		0
Recurrent N stage†‡		
rN0		10 (66.7%)
rN1		3 (20%)
rN2		2 (13.3%)
rN3		0
Time from completion of primary treatment to recurrence (days)†		654 (217-1954)

Abbreviation: WHO = World Health Organization.
* Data are shown as No. (%) of patients or median (range).
† Staging according to Union for International Cancer Control TNM classification 7th edition.
‡ Applicable only to patients with recurrent disease.

based), with a median cumulative cisplatin dose of 160 mg/m^2 (range, 100-300 mg/m^2); 12% of patients received adjuvant chemotherapy with cisplatin and 5-fluorouracil (PF), while 10% of patients received induction chemotherapy (PF). Table 2 summarises the details of the primary treatment courses.

For residual disease, the median prescribed FSRT dose was 18 Gy (range, 12-18 Gy), delivered in a median of three fractions (range, 2-3 fractions), with a median fractional dose of 6 Gy (range, 5-6 Gy). The median BED_{10} was 28.8 Gy_{10} (range, 19.2-28.8 Gy_{10}) and that of EQD2 was 24 Gy (range, 16-24 Gy). For recurrent disease, when FSRT was used alone, the median prescribed dose was 48 Gy (range, 14-48 Gy), delivered in a median of 6 fractions (range, 2-6 fractions), with a median fractional dose of 8 Gy (range, 6-8 Gy). In two patients, FSRT was used as a tumour boost on top of a long conventional fractionated reirradiation IMRT of 50 to 60 Gy. The median BED_{10} was 86.4 Gy_{10} (range, 48-120 Gy_{10}) and that of EQD2 was 72 Gy (range, 40-100 Gy). Figure 1 illustrates details of the setup and planning of FSRT. Table 3 summarises the FSRT treatment parameters.

Table 2. Characteristics of primary treatment course.*

	Residual disease (n = 34)	Recurrent disease (n = 15)
Technique		
IMRT	33 (97.1%)	11 (73.3%)
2D conventional RT	0	3 (20%)
Unknown	1 (2.9%)	1 (6.7%)
Dose to gross tumour/ lymphadenopathy (Gy)		
70	33 (97.1%)	11 (73.3%)
72	1 (2.9%)	0
66	0	4 (26.7%)
No. of fractions		
33	20 (58.8%)	8 (53.3%)
35	13 (38.2%)	7 (46.7%)
36	1 (2.9%)	0
Time from pathological diagnosis to completion of RT (days)	92 (62-168)	97 (57-169)
Concurrent chemotherapy		
Cisplatin 40 mg/m^2 weekly	14 (41.2%)	7 (46.7%)
Cisplatin 100 mg/m^2 q3wks	3 (8.8%)	0
Carboplatin	2 (5.9%)	0
None	15 (44.1%)	8 (53.3%)
Concurrent cumulative cisplatin dose (mg/m^2)	160 (100-300)	200 (160-240)
Use of induction chemotherapy	4 (11.8%)	1 (6.7%)
Use of adjuvant chemotherapy	5 (14.7%)	1 (6.7%)

Abbreviations: 2D = two-dimensional; IMRT = intensity-modulated radiation therapy; q3wks = every 3 weeks; RT = radiotherapy.
* Data are shown as No. (%) of patients or median (range).

Response and Local Control Rates

The pathological complete response rate was 82.3% for the residual disease group. For the recurrent disease group, 93.3% achieved radiological shrinkage, with pathological complete response achieved in 60%. The actuarial 3-year local control rates were 78.9% and 68.2% for the residual and recurrent disease groups, respectively. Overall, for the eight patients who failed to achieve local control after FSRT, five had successful salvage surgery, one developed bone metastases, one had extensive inoperable neck failure, and one relapsed locally again 1 year after reirradiation with disease too advanced for further salvage.

Survival Outcomes

For the residual disease group, the median PFS was 66.1 months, median OS was 102.0 months, and median DSS was not reached with our length of follow-up. Similar to local control rates, the recurrent disease group had inferior outcome, with median PFS of 29.3 months, median OS of 33.2 months, and median DSS of 40.9 months.

The actuarial 3-year PFS, DSS, and OS for the residual disease group were 66.2%, 82.2%, and 74.0%, respectively. For the recurrent disease group, the PFS, DSS, and OS were 40.0%, 58.7%, and 46.7%, respectively. Upon log-rank testing, the residual disease group had superior survival outcome after FSRT compared with the recurrent disease group, and the difference was statistically significant across all three endpoints (Figure 2).

Prognostic Factors

The cut-off values of FSRT GTV as a predictor for survival outcomes of the residual and recurrent disease groups were found to be 16 mL and 10 mL, respectively.

FSRT GTVs of ≤16 mL for the residual disease group, and that of ≤10 mL for the recurrent disease group were associated with longer PFS and OS (Figure 3). N3 nodal staging status was associated with poorer PFS in the residual disease group. Other factors, including advanced initial T stage (T3-4 vs. T1-2) in patients in the residual disease group, and recurrent T stage (rT3-4 vs. rT1-2) in patients in the recurrent disease group showed only trends to inferior outcome in PFS or OS but were not statistically significant prognostic factors (Table 4).

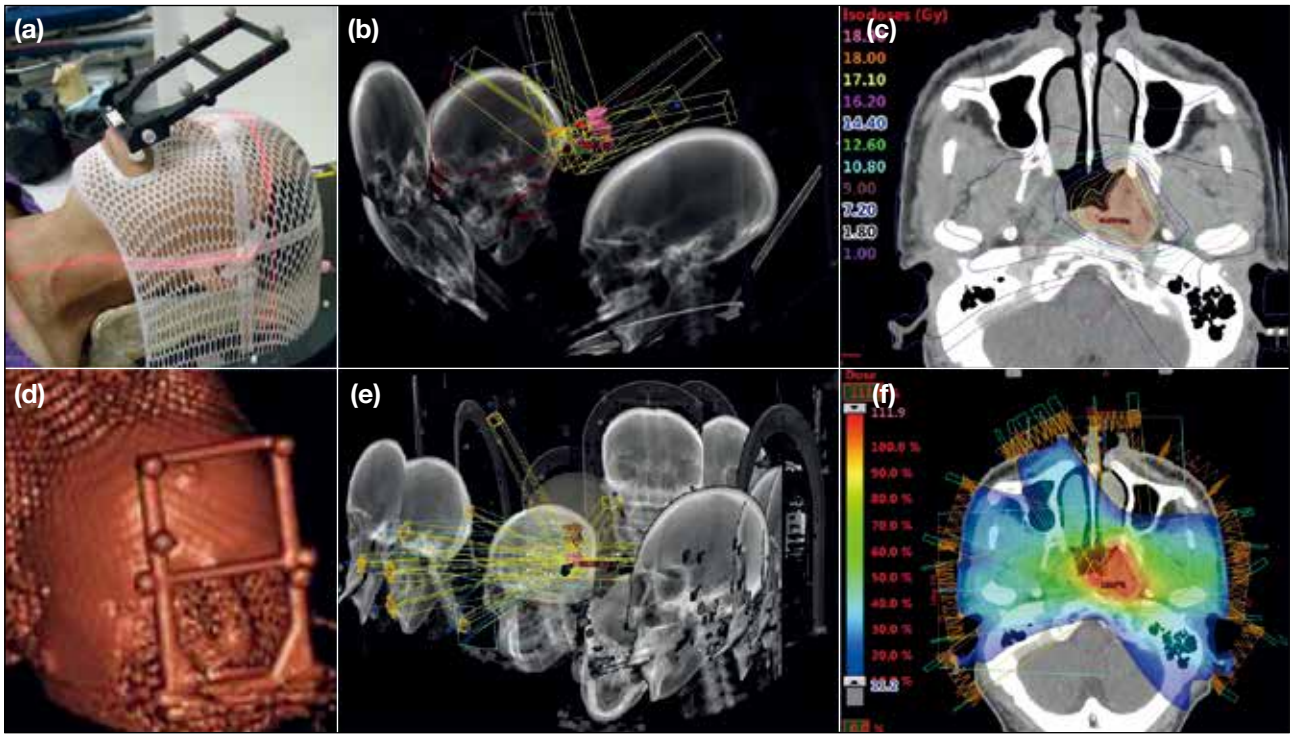

Figure 1. (a) Patient immobilised in tailor-made precision thermoplastic cast (Orfit [Wijnegem, Belgium]); (b) Zmed (Holliston [MA], United States) frameless stereotactic localisation system, which utilises a bite tray with reflective fiducial arrays plus a ceiling-mounted three-dimensional infrared camera for optical localisation and tracking; (c) field designs of a multileaf collimation (MLC)–based fractionated stereotactic radiotherapy (FSRT) treatment (all except one of our patients received MLC-based treatment); (d) field designs of a cone-based FSRT treatment; (e, f) dose distributions of an MLC-based FSRT plan for a patient with persistent disease in the left nasopharynx. The 18-Gy (100%) isodose line (orange) covered the planning target volume (yellow) well and the brainstem received a maximum of only 1 Gy in this reirradiation course.

Table 3. Treatment parameters of reirradiation fractionated stereotactic radiotherapy course.*

	Residual disease (n = 34)	Recurrent disease (n = 15)
Technique		
SRT alone	34 (100%)	13 (86.7%)
SRT + IMRT	0	2 (13.3%)
MLC- or cone-based		
MLC	33 (97.1%)	15 (100%)
Cone	1 (2.9%)	0
GTV (mL)	12.8 (4.6-66.8)	15.9 (2.1-74.9)
Total prescribed dose (Gy)	18 (12-18)	48 (14-48)
Fractional dose (Gy)	6 (5-6)	8 (6-8)
No. of fractions	3 (2-3)	6 (2-6)
Time/dose/fractionation		
18 Gy in 3 fr, 2 fr per week	31 (91.2%)	0
12 Gy in 2 fr, 2 fr per week	2 (5.9%)	0
15 Gy in 3 fr, 2 fr per week	1 (2.9%)	0
48 Gy in 6 fr, 2 fr per week	0	11 (73.3%)
30 Gy in 5 fr, 2 fr per week	0	1 (6.7%)
IMRT 50 Gy/25 fr + SRT tumour boost 14 Gy/2 fr	0	1 (6.7%)
IMRT 60 Gy/30 fr + SRT boost 30 Gy/5 fr	0	1 (6.7%)
SRT 32 Gy/4 fr then 15 Gy/3 fr	0	1 (6.7%)
Biologically effective dose with α/β = 10 Gy (Gy_{10})	28.8 (19.2-28.8)	86.4 (48-120)
Equivalent total dose in 2-Gy fr (Gy)	24 (16-24)	72 (40-100)

Abbreviations: fr = fraction; GTV = gross tumour volume; IMRT = intensity-modulated radiation therapy; MLC = multileaf collimation; SRT = stereotactic radiotherapy.

* Data are shown as No. (%) of patients or median (range).

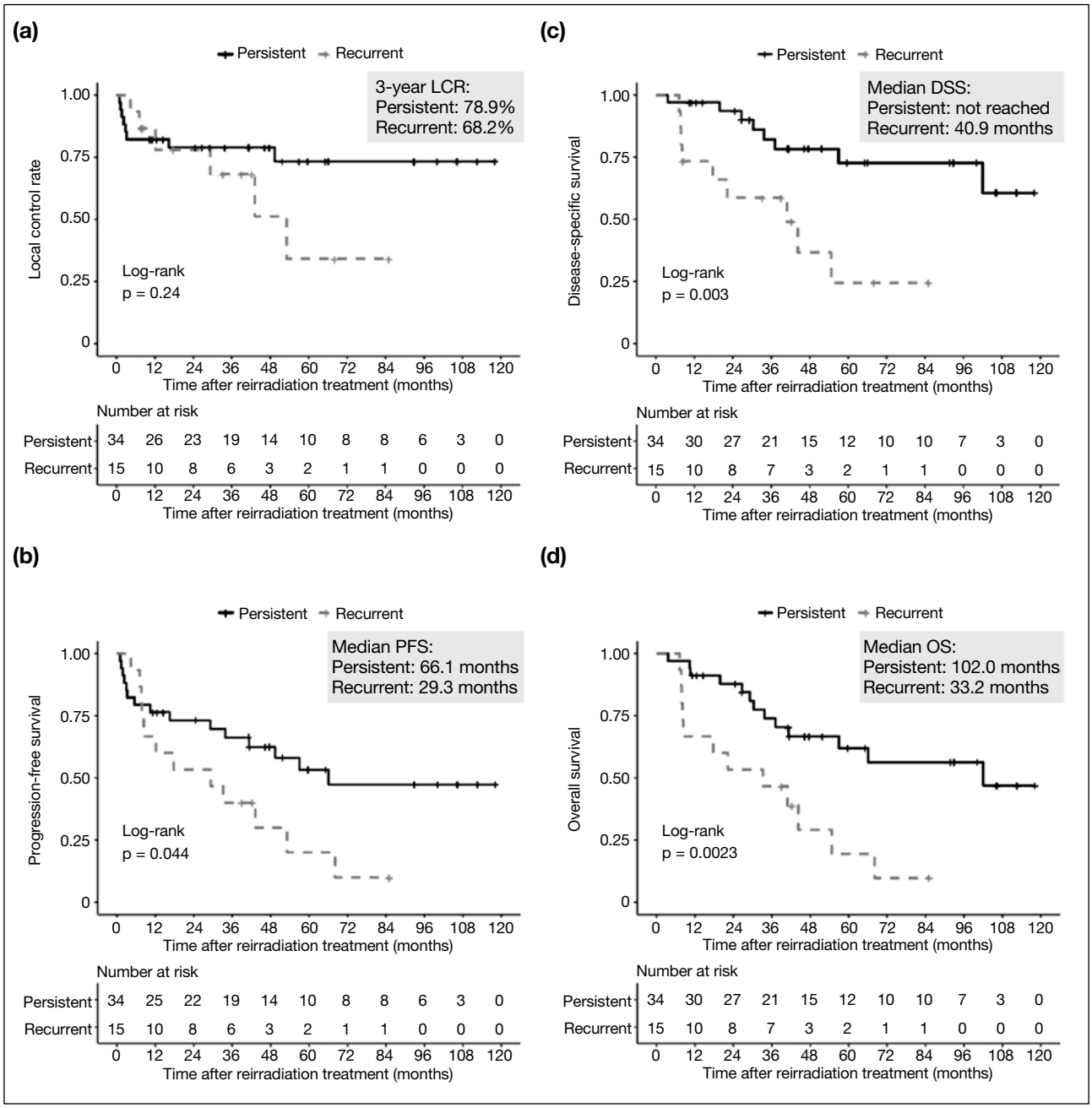

Figure 2. Kaplan-Meier curves and 3-year actuarial rates by type of local failure. Log-rank tests were performed to test for statistical differences: (a) local control rate (LCR); (b) progression-free survival (PFS); (c) disease-specific survival (DSS); and (d) overall survival (OS).

Complications

All patients were able to complete the scheduled FSRT. No significant acute complications occurred. Thirteen severe late complications occurred in 12 patients (24%) after FSRT. The incidence of severe late complications was higher in the recurrent disease group (in 6 patients, 40%) than in the residual disease group (18%).

Overall, five patients (10%) developed massive haemorrhage and all died of this event. Among them, two had unsalvageable locoregional disease and the haemorrhage could have been due to disease progression. All of these haemorrhagic events happened within 5 years of primary RT, and within 3 years of reirradiation FSRT. Other known severe late complications associated with reirradiation, including temporal lobe necrosis, cranial nerve palsy, mandible/maxilla radionecrosis, and local mucosal necrosis all occurred at a rate of <5%. One patient

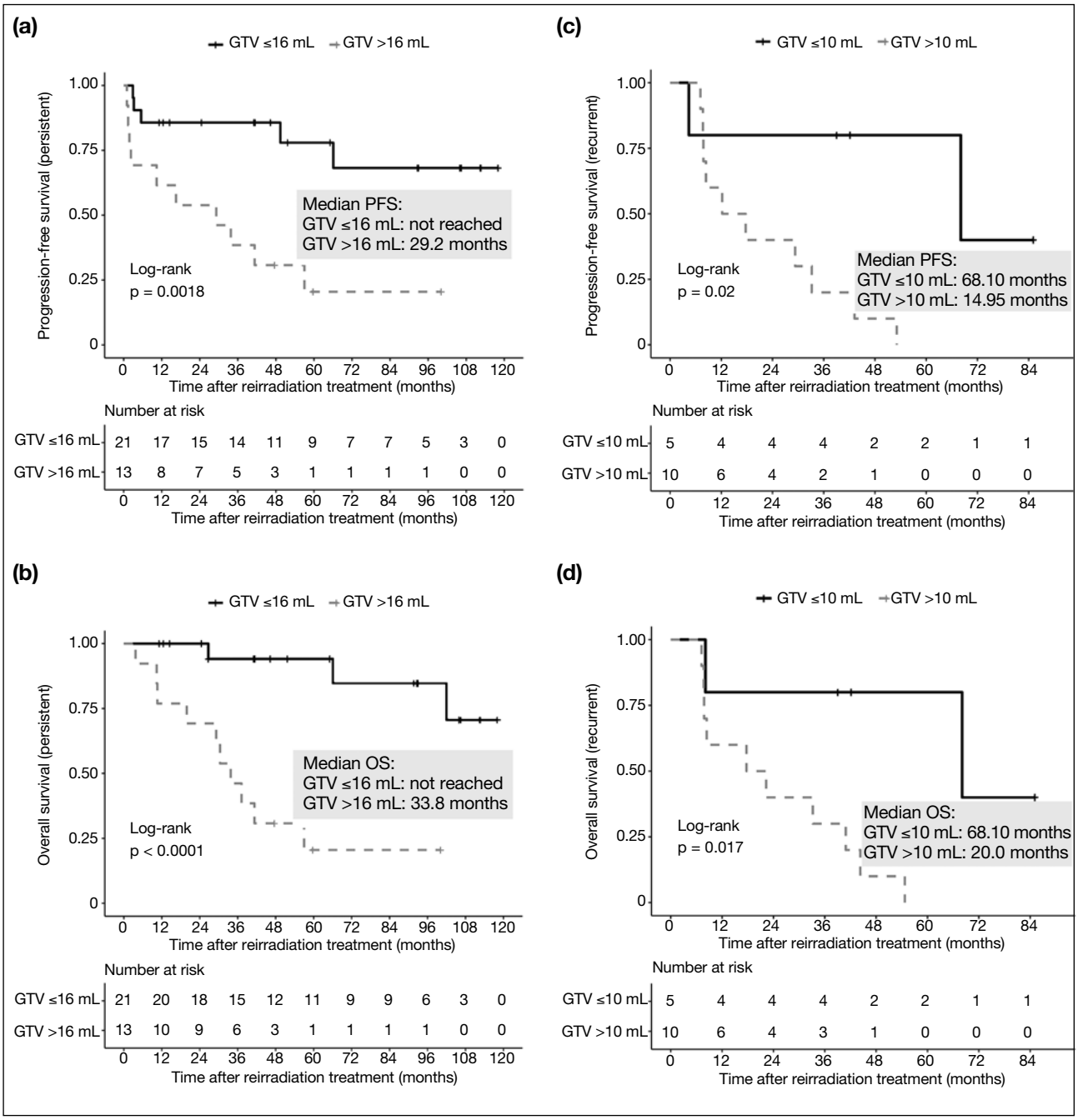

Figure 3. (a) Progression-free survival and (b) overall survival of persistent (residual) disease group stratified by gross tumour volume with a cut-off of 16 mL. (c) Progression-free survival and (d) overall survival of recurrent disease group stratified by gross tumour volume with a cut-off of 10 mL.

who had undergone a salvage nasopharyngectomy with the maxillary swing approach after failing local control with FSRT developed C1/2 osteomyelitis complicated by an epidural abscess and meningitis 2 years later but survived the event. Details of severe toxicities are shown in Table 5.

DISCUSSION

Treatment options for NPC with local failure can be operative or non-operative. Important distinctions exist between residual and recurrent disease, with better survival and disease control rates for those with residual disease. This finding is consistent across multiple

Table 4. Association with overall survival and progression-free survival for residual disease group and recurrent disease group.

Residual disease	Overall survival		Progression-free survival	
	HR_{unadj} (95% CI)	p Value	HR_{unadj} (95% CI)	p Value
Age	1.03 (0.98-1.08)	0.214	1.02 (0.98-1.07)	0.368
Female sex	1.44 (0.44-4.72)	0.544	2.56 (0.87-7.51)	0.087
MRI T3/4 (ref T1/2)*	1.30 (0.39-4.27)	0.670	1.04 (0.35-3.09)	0.940
MRI N3 (ref N0/1/2)*	5.38 (0.59-48.8)	0.135	5.13 (1.03-25.6)	0.046
GTV >16 mL	12.84 (2.69-61.2)	0.001	4.87 (1.63-14.5)	0.005
BED_{10} (Gy_{10})	1.06 (0.85-1.33)	0.605	1.08 (0.87-1.35)	0.486
Recurrent disease	**Overall survival**		**Progression-free survival**	
	HR_{unadj} (95% CI)	p Value	HR_{unadj} (95% CI)	p Value
Age	1.03 (0.97-1.09)	0.335	1.03 (0.97-1.09)	0.330
Female sex	0.29 (0.06-1.38)	0.119	0.27 (0.06-1.30)	0.103
MRI T3/4 (ref T1/2)*	2.18 (0.69-6.91)	0.184	2.46 (0.77-7.84)	0.128
MRI N3 (ref N0/1/2)*	6.48 (0.59-71.6)	0.127	4.14 (0.43-39.9)	0.219
GTV >10 mL	8.41 (1.06-66.8)	0.044	8.16 (1.02-65.3)	0.048
BED_{10} (Gy_{10})	1.00 (0.96-1.05)	0.832	1.00 (0.96-1.04)	0.940
Cumulative cisplatin dose	1.01 (0.98-1.03)	0.718	1.01 (0.98-1.03)	0.622
Recurrent T3/4 (ref T1/2)	3.13 (0.82-11.9)	0.094	3.54 (0.93-13.5)	0.065

Abbreviations: 95% CI = 95% confidence interval; BED_{10} = biologically effective dose with α/β = 10 Gy; GTV = gross tumour volume; HR_{unadj} = unadjusted hazard ratios; MRI = magnetic resonance imaging.
* MRI staging at first presentation.

Table 5. Severe late toxicities attributable to reirradiation.

	Residual disease (n = 34)	Recurrent disease (n = 15)
Fatal haemorrhage	1 (3%)	4 (27%)
Temporal lobe necrosis	2 (6%)	0
Mandible/maxilla radionecrosis	1 (3%)	1 (7%)
Local mucosal necrosis	1 (3%)	0
Cranial nerve palsy	0	2 (13%)
C1/2 osteomyelitis complicated with epidural abscess, meningitis	1 (3%)	0
Total	6 (18%)	7 (47%)*

Abbreviation: C1/2 = cervical spine level 1 and 2.
* Developed in 6 patients.

studies in the literature. It remains unclear whether there is a relationship between tumour biology and poorer reirradiation response of recurrent disease, i.e., revival of cancer cells, compared with residual disease, which could be due to marginal miss of boost dose, or prolonged/ incomplete regression. In our study, although patients with residual and recurrent disease were treated with a similar salvage RT technique, the radiation doses they received were vastly different, and they were mostly analysed as two distinctive groups.

For residual disease, in particular for early-stage disease (rT1-2), treatment results and survival rates were highly favourable and comparable to patients who had had a complete response after the first treatment course. Various salvage options including surgery, further radiation boost by external beam RT or brachytherapy, or photodynamic therapy all result in good and comparable response rates.[3,14-24] Recurrent disease, however, is associated with issues of radioresistance and higher morbidity with irradiation, thus surgery is often preferred when it is technically feasible. A matched cohort analysis showed that salvage endoscopic nasopharyngectomy might be superior to IMRT in terms of survival outcome, quality-of-life benefits, and complication rates for selected rT1-T3 NPC.[25] Nonetheless, there has been no direct prospective comparison between different techniques of nasopharyngectomy with various non-operative approaches, and such trials would not be feasible in a randomised, well-stratified manner without large-scale multi-centre cooperation and stringent quality control. Besides, it is important to recognise that each approach has its unique advantages and shortcomings and the treatment decision has to take multiple factors into account, such as the location and extent of disease, availability of modality and expertise, patient preference, and co-morbidities. Table 6 summarises the characteristics of different treatment approaches in salvage treatment of NPC.[3,14-24]

Our study provides updated data on the efficacy of LINAC-based FSRT, using a frameless stereotactic system and IMRT technique, in treating patients with

Table 6. Overview of different treatment approaches in salvage treatment of nasopharyngeal carcinoma.

Modalities	Characteristics	Complications of note
Nasopharyngectomy[15,16] • Open • Endoscopic • Robotic-assisted	• Highly specialised surgery, required expertise due to complex anatomy • Surgery can only be curative if the tumour is radically removed, thus feasible only for rT1-2 to limited rT3 disease, and also no carotid artery involvement • No concern on radioresistance • Endoscopic/robotic-assisted technique: minimally invasive, good visualisation but had to overcome the issues of limited instrumentation space • If positive margin resection, may consider postoperative RT or chemotherapy	More reported with open approaches: • Palatal defect, osteonecrosis, flap necrosis • Osteomyelitis, meningitis • Facial scarring, trismus • Dysphagia, aspiration • Carotid bleeding
External beam RT • SRS • FSRT • IMRT[3,14,17-19]	• Non-invasive • High-precision RT techniques are preferred, so to allow a rapid dose fall-off from tumour targets to normal at-risk organs in proximity • Flexible strategies allow treatment for advanced recurrence: IMRT could deliver different dose levels to avoid surrounding vital structures; SRS, FSRT could be used as boost dose	Associated with reirradiation: • Neurological: radiation myelitis, temporal lobe necrosis, cranial nerve palsies • Carotid pseudoaneurysm • Soft tissue and bone necrosis • Radiation osteomyelitis (skull base, cervical spine) • Endocrine dysfunction
Brachytherapy[20-23] • Intracavitary: iridium (Ir-192) after loading • Interstitial: gold (Au-198) grain implant	• Delivers high radiation dose to targets with a rapid dose fall-off to preserve surrounding normal tissues • Due to short range, only recommended for persistent/ recurrent T1 disease in current practice • Interstitial — some locations, e.g., cartilage of the Eustachian tube crus are not assessable to the gun applicator • Could be used as a dose boost	
Photodynamic therapy[24]	• Illuminate tumour with a non-thermic laser after IV injection of photosensitiser • Effective treatment depth with second-generation photosensitisers (e.g., temoporfin) is 10 mm: recommended for T1/2 disease <10 mm depth (more data for residual disease) • No radiation toxicities. Treatment easy to deliver and repeatable	• Headache • Photosensitivity • Tinnitus, middle ear effusion

Abbreviations: FSRT = fractionated stereotactic radiotherapy; IMRT = intensity-modulated radiation therapy; IV = intravenous; rT = Union for International Cancer Control TNM classification; RT = radiotherapy; SRS = stereotactic radiosurgery.

NPC with local failure after high-dose primary IMRT. The frameless system based on live tracking of fiducials was non-invasive, required no neurosurgical expertise, and improved patients' comfort compared with the conventional frame-based technique. Moreover, our study findings are highly relevant to contemporary practice as almost all of our patients received IMRT (now the standard of care in many countries) as their primary treatment. In fact, it has been proposed that with the prevailing use of IMRT, the nature of recurrences is likely to be different from those in patients in the older era of two-dimensional or three-dimensional conformal RT, when patients with NPC may have failed locally due to marginal misses or underdosing to the clinical targets. In the setting of modern imaging and RT techniques, local recurrence after high-dose RT may instead be accounted for by the presence of populations of radioresistant cancer cells that survive the initial course of treatment and may pose a new set of challenges for salvage. Therefore, previous results of salvage RT after conventional techniques may not be as readily applicable for patients treated in the IMRT era.[14,26] From the overall results of our study, in spite of these differences, our clinical outcomes are comparable to previously reported FSRT studies in the literature (Table 7[22,27-37]).

On reviewing patients who suffered from fatal nasopharyngeal haemorrhage as a complication, all of these patients presented first with sentinel bleeds up to 2 months before their fatal episode, suggesting the possibility of earlier detection of carotid artery pseudoaneurysms by raising physicians' and patients' awareness, especially in patients with known risk factors such as reirradiation and skull base radionecrosis.[38] Earlier detection may allow preventive endovascular interventions to be performed.

Table 7. Literature review of stereotactic reirradiation studies for nasopharyngeal carcinoma (only included studies with retrievable full text via PubMed or journal webpages).

First author	No. of cases	Reirradiation technique and dose (Gy)	Local control*	Survival*	Major complications
Orecchia, 1999[30]	R: 13 (rT1-4)	FSRT 24 Gy in 2-4 fr	Radiological CR 38%	3-y OS 31%	Nil
Ahn, 2000[31]	R: 12 (no staging info)	FSRT 45-65 Gy, 2.5-3 Gy/fr	2 y 92%	2-y OS 60%	Nil
Xiao, 2001[32]	P: 32 R: 18 (rT1-4)	FSRT 14-35 Gy, 6-8, 12, or 15 Gy/fr, ± external beam RT	Not reported	3-y OS 60% 3-y DFS 74%	FH 16%
Pai, 2002[33]	R: 36 (rT1-4)	3DCRT 20-60 Gy + SRS 8-20 Gy	3 y 56%	3-y OS 54%	LMN 11%
Chua, 2003[34]	P: 7 R: 11 (rT1-2)	SRS 11-14 Gy	2 y 72%	2-y OS 86% P: 2-y LFFS 100% R: 2-y LFFS 55%	TLN 6%
Chua, 2005[35]	R: 31 (rT1-4)	IMRT 50-60 Gy in 25-30 fr ± SRS 8.5-12.6 Gy boost in around 1/3 of patients (who had rT3-4 disease with D_{min} of PTV <45 Gy)	1 y 56%	1-y OS 63%	CNP (10%), brain necrosis (7%), soft tissue fibrosis (3%), grade ≥3 ototoxicity (10%)
Low, 2006[22]	P: 5 R: 31 (rT1-2)	SRS 18 Gy + BT 12 Gy in 2 fr	P: 5 y 100% R: 5 y 57%	P: 5-y OS 100% R: 5-y OS 53%	CNP 20%, TLN 8%, skull base osteonecrosis (17%), palatal fibrosis (17%), trismus (20%)
Wu, 2007[27]	P: 34 R: 56 (rT1-4)	P: FSRT 10-24 Gy in 2-4 fr R: FSRT 12-49 Gy in 2-8 fr	P: 3 y 89% R: 3 y 75%	P: 3-y DSS 81% R: 3-y DSS 46%	FH (2%), TLN (7%), brainstem necrosis (3%), LMN (7%)
Seo, 2009[28]	R: 35 (rT1-4)	FSRT 24-45 Gy in 3-5 fr	LFFS reported	5-y OS 60% 5-y LFFS 79%	FH (6%), LMN (6%)
Ozyigit, 2011[29]	R: 24 (rT1-4)	FSRT 30 Gy in 5 fr	2 y 82%	2-y CSS 64%	Carotid blowout syndrome (17%), CNP (12%), brain necrosis (4%)
Liu, 2013[36]	P: 136	FSRT 8-32 Gy in 2-8 fr	LFFS reported	3-y LFFS 95% 5-y OS 76%	FNH (3.7%), CNP (6%), TLN (4.4%),
Dizman, 2014[37]	R: 24 (rT1-4)	FSRT 25-30 Gy in 5 fr	3 y 21%	3-y OS 31%	Grade 4 acute mucositis (4%), TLN (4%)
Current	P: 34 R: 15 (rT1-3)	P: FSRT 12-18 Gy in 2-3 fr R: FSRT 14-48 Gy in 2-6 fr	P: 3 y 79% R: 3 y 68%	P: 3-y DSS 82%, 3-y OS 74% R: 3-y DSS 59%, 3-y OS 47%	FH (10%), CNP (4%), TLN (4%), LMN (2%), osteonecrosis (4%), osteomyelitis (2%)

Abbreviations: 3DCRT = three-dimensional conformal radiotherapy; BT = brachytherapy; CNP = cranial nerve palsy; CR = complete response; CSS = cancer-specific survival; D_{min} of PTV = minimum dose received by planning target volume; DFS = disease-free survival; DSS = disease-specific survival; FH = fatal haemorrhage; FNH = fatal nasopharyngeal haemorrhage; fr = fraction; FSRT = fractionated stereotactic radiotherapy; IMRT = intensity-modulated radiation therapy; LFFS = local failure-free survival; LMN = lower motor neuron; NPC = nasopharyngeal carcinoma; OS = overall survival; P = persistent NPC; R = recurrent NPC; rT = Union for International Cancer Control TNM classification; RT = radiotherapy; SRS = stereotactic radiosurgery; TLN = temporal lobe necrosis.
* Percentage values rounded up to the nearest whole number.

As our study only included a limited number of patients and survival events, conclusions regarding prognostic factors should be drawn with caution, given the known limitations of variable analyses of small cohorts. Nonetheless, in the residual disease group, we found an impact of FSRT GTV with a cut-off of 16 mL on OS and PFS, similar to findings reported in many previous studies.[27,39-41] The cut-off values of this GTV in relation to survival outcomes for the residual and recurrent disease groups identified by receiver operating characteristic analysis were different (16 mL and 10 mL, respectively). We postulate that this difference could be due to the inherently poorer radiosensitivity of recurrent disease. For the recurrent disease group, given the very limited number of patients in the cohort, variable analysis was more underpowered and might explain why some commonly reported important prognostic factors such as rT stage[28,29] failed to reach statistical significance, and the significance value of GTV was just below 0.05 ($p = 0.044$ for OS, $p = 0.048$ for PFS). However, on careful assessment of all the regression analysis results, the hazard ratios and p values of FSRT GTV far outweigh those of either initial or recurrent T stage in both groups. Over the years, much effort has been made to formulate prognostic algorithms to predict radioresistance in recurrence, so that low-risk patients could be confidently

treated with reirradiation, whereas the unfavourable high-risk group may be managed more aggressively or recruited into clinical trials.[42,43] With the changing patient population and treatment advancements, the prognostic effects of different factors could be dynamic and should be continuously examined.

Looking to the future, the use of charged-particle RT, including intensity-modulated ion therapy (IMIT) and intensity-modulated proton therapy (IMPT), potentially offers physical and biologic advantages over photon-based IMRT. The multicentric in silico ROCOCO trial has demonstrated further reduced doses to OARs using IMIT or IMPT compared with photon therapy.[44] Very recently, various group had been studying intensity-modulated carbon ion RT in clinical practice for salvage reirradiation of NPC, and has published promising early results.[45,46] However, long-term follow-up is needed to assess the long-term outcome and late toxicities, and also the optimal dose and fractionation.

CONCLUSION

In summary, we have presented our findings on the efficacy and safety of LINAC-based FSRT, using a frameless stereotactic system and IMRT technique, in treating patients with NPC with local failure (including residual and recurrent disease) after high-dose primary IMRT. Using this less-invasive and resource-friendly technique, the clinical outcomes were comparable to those in the literature. FSRT GTV was identified as a predictor of PFS and OS in patients irradiated for residual disease. We look forward to more studies reporting outcomes of reirradiation for patients treated in the IMRT era, and also eagerly await long-term results from IMIT and IMPT, which may further raise the therapeutic ratio and overcome the existing barriers to reirradiation.

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