Original Article

The treatment modalities and outcomes of recurrent nasopharyngeal carcinoma: a retrospective cohort study in the modern era

Ju-Chun Chien[1], Chien-Yu Huang[2], Yu-Chang Hu[1], Kuo-Chen Chang[1], Kuo-Ping Chang[2,3], Bor-Hwang Kang[2,4], Wen-Shan Liu[1,4]

[1]Department of Radiation Oncology, [2]Department of Otorhinolaryngology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [3]School of Medicine, National Yang-Ming University, Taipei, Taiwan; [4]School of Medicine, National Defense Medical Center, Taipei, Taiwan

Contributions: (I) Conception and design: JC Chien, CY Huang, KP Chang, WS Liu; (II) Administrative support: JC Chien, YC Hu, KC Chang, BH Kang, WS Liu; (III) Provision of study materials or patients: YC Hu, KC Chang, KP Chang, BH Kang; WS Liu; (IV) Collection and assembly of data: JC Chien, KC Chang, YC Hu; (V) Data analysis and interpretation: JC Chien, CY Huang, WS Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wen-Shan Liu. School of Medicine, National Defense Medical Center, No. 386, Dazhong 1st Rd., Zuoying Dist., Kaohsiung City 81362, Taiwan. Email: wsliu@vghks.gov.tw.

Background: While chemoradiotherapy being widely recognized as primary treatment for nasopharyngeal carcinoma (NPC), optimal salvage modalities for locoregionally recurrent NPC (LRrNPC) are still under debate. This study aimed to explore outcomes of different salvage modalities for LRrNPC.

Methods: Non-metastatic LRrNPCs were retrospectively recruited. Clinical factors and salvage treatments were evaluated. The primary and secondary endpoint were locoregional-progression-free survival (LRPFS) and overall survival (OS), respectively. Outcomes were compared among re-irradiation (reRT), surgical resection (SR), combination therapy (SR + reRT), and systemic treatment only (STx).

Results: From 2006–2017, 29 consecutive LRrNPCs were enrolled, including 37.9% rT1-2 and 62.1% rT3-4 diseases. Salvage treatments included 14 reRT, 6 SR, 6 SR + reRT, and 3 STx. All re-irradiations were intensity-modulated radiotherapy (IMRT) and 83.3% SRs were done by endoscopic approach. After median follow-up of 36 months, the 3-year LRPFS was 56.5% and 3-year OS was 64.1%. When compared to STx, reRT and SR + reRT both showed superior LRPFS (re-RT, HR: 0.06, P=0.009; SR + reRT, HR: 0.07, P=0.021, adjusted for rT), while SR revealed no significant benefit. However, there was no significant difference in LRPFS among the three local treatment modalities. Severe complication rates were 51.7% for ≥grade 3 and 6.9% for grade 5.

Conclusions: For LRrNPCs, locoregional treatments including reRT and SR + reRT might have additional local control benefit from systemic therapy. The risk of fatal toxicity decreased with increasing use of IMRT and endoscopic resection. Considering the limited case number and retrospective design, prospective trials are warranted to further evaluate the efficacy and safety.

Keywords: Endoscopic resection; recurrent nasopharyngeal carcinoma (NPC); re-irradiation

Received: 20 February 2019; Accepted: 15 July 2019; published: 26 July 2019.
doi: 10.21037/tro.2019.07.02
View this article at: http://dx.doi.org/10.21037/tro.2019.07.02

Introduction

Nasopharyngeal carcinoma (NPC) is considered as a rare malignancy in most of the countries (1). But the incidence is much higher in East and Southeast Asia, including Taiwan, which has an average annual incidence of 5.1 per hundred-thousand people during 2010–2015 (2,3). While the role of chemoradiotherapy for treatment-naïve NPC being well established, the optimal treatment choice for locoregionally recurrent NPC (LRrNPC) is still under debate (4-8).

According to published literatures, re-irradiation and surgical resection (SR) have been two major treatment options for residual or recurrent NPC. The 5-year local control rate of LRrNPC receiving re-irradiation and surgical treatment ranged from 15–85.5% and 40–85.5%, respectively (7-11). The high heterogeneity among studied populations in recurrent stage, nodal recurrence, or disease-free interval may be the reasons of quite different results from studies (7,12-17). Severe complication rates up to 65.5% is also challenging in retreating LRrNPC (18-21). Omitting locoregional treatment has also been proposed considering the lack of survival benefit and high complication rate (22). However, with the critical location of nasopharynx, not only treatment-related adverse event but also locoregional disease progression might deteriorate the quality of life of patients.

Among recent literatures reporting comparative outcomes, You *et al.* reported a superior 5-year survival rate of 77.1% with endoscopic resection comparing to 55.5% with re-irradiation by IMRT in resectable T1-T3 LRrNPCs. Nevertheless, a high treatment-related mortality rate of 34.7% in the re-irradiated early recurrent NPCs might overshadow the potential benefit of re-irradiation (18). In another observational study, Weng *et al.* suggested an additional survival benefit when combining endoscopic resection with chemoradiotherapy in treating residual or recurrent NPCs (23). Yet, 91.7% of the adjuvant chemoradiotherapies were performed following margin-free resections. In consideration of severe complications and lack of surgical control group, this might limit the extrapolation of the results (23).

With detail review of medical records and long-term follow-up, this study aimed to evaluate outcomes of different treatment modalities in LRrNPC patients.

Methods

Study cohort and endpoint definition

Patients with LRrNPC diagnosed in single medical center who had achieved a complete remission after first treatment course, proven by endoscopic or image study, with disease-free interval greater than 6 months were enrolled. Those who had residual disease, known distal metastasis, and other malignant disease were excluded. Patients' characteristics including sex, age, recurrent stage, disease free interval, salvage treatment, and survival data were retrospectively collected from medical charts, hospital cancer registry records, and the National Death Registry.

Outcomes were calculated from the date of recurrence diagnosed to the date of sequential events recorded. The primary endpoint was locoregional-progression-free survival (LRPFS), which was defined as no progression recorded on subsequent image or endoscopic examinations. The secondary endpoint was overall survival (OS). For the severe adverse events, fatal acute complications and severe late complications limited to osteoradionecrosis, temporal lobe necrosis, and dysphagia causing frequent aspiration pneumonia or long-term feeding tube dependence were identified during follow-up course.

The study protocol had been registered and verified by the institutional review board (VGHKS18-CT11-11).

Statistical analysis

The software Statistical Package for Social Science, 20th edition (SPSS 20th) was used for data analysis. The baseline characteristics between treatment groups were compared using the Pearson's chi square test. Factors imbalanced among treatment groups would be adjusted in further analysis. For survival outcomes, the Kaplan-Meier method was performed. Cox regression model was used to recognize possible prognostic factors. Logistic regression was performed to evaluate risk factors for severe adverse events. Factors achieving a P value <0.15 in univariate analysis were kept for multivariate test (24). And a P value <0.05 was considered statistically significant.

Results

Patients inclusion and treatment modalities

From 2006–2017, 31 consecutive patients were identified with distal-metastasis-free LRrNPC. Recurrences were diagnosed with pathological proof in 86.2% of the cases. Others were diagnosed by serial image studies including PET/CT or MRI and clinical judgement. PET/CT was performed in 39.3% cases to rule-out distal metastasis

Table 1 Baseline characteristics at recurrence of the patients in salvage treatment groups

Parameters	SR (n=6)	reRT (n=14)	SR + reRT (n=6)	STx (n=3)	P
Sex					0.539
Male (n=25)	5	11	6	3	
Female (n=4)	1	3	0	0	
Age, years					0.512
≤65 (n=27)	6	12	6	3	
>65 (n=2)	0	2	0	0	
Initial RT					0.512
2D/3D (n=8)	1	5	1	1	
IMRT/Arc (n=21)	5	9	5	2	
rT classification					0.004
rT1-2 (n=11)	6	4	1	0	
rT3-4 (n=18)	0	10	5	3	
rN classification					0.718
N0 (n=21)	4	10	4	3	
N+ (n=8)	2	4	2	0	
r-stage (AJCC 7th)					0.004
Stage I-II (n=11)	6	4	1	0	
Stage III-IV (n=18)	0	10	5	3	
Disease-free interval†					0.135
6–12 months (n=7)	1	3	3	0	
12–36 months (n=13)	5	4	2	2	
>36 months (n=9)	0	7	1	1	
Year of recurrence					0.491
2006–2012 (n=9)	2	4	3	0	
2013–2017 (n=20)	4	10	3	3	

†, disease-free interval refers to the duration from the end of first course of treatment to diagnosis time of recurrence. SR, surgical resection; reRT, re-irradiation; STx, systemic treatment; RT, radiotherapy; 2D/3D RT, 2-dimensional or 3-dimensional conventional radiotherapy; IMRT/VMAT, intensity-modulated radiotherapy or volumetric modulated Arc radiotherapy.

and whole body bone scan, chest image, and abdominal sonogram were used as substitute in 60.7% cases. While 2 were excluded for not receiving any treatment, 29 cases were enrolled for the final analysis, including 37.9% rT1-2 and 62.1% rT3-4. 34.5% of the cases had concurrent nodal recurrences and 72.4% had IMRT for the initial NPC treatment.

Twenty-six patients had received locoregional treatments, consisting of 14 re-irradiations (reRT), 6 SRs, and 6 combinations of surgery and re-irradiation (SR + reRT). The baseline characteristics of enrolled cases and their distribution among treatment modalities were shown in *Table 1*. Cases with early recurrences were inclined to have SR and most of those with advanced recurrences underwent re-irradiation. For SR, endoscopic approach accounted for 83.3% of the operations and a confident free-margin was achieved in 66.7% of rT1-2 and 33.3% of rT3-4 cases. Adjuvant re-irradiations were performed in cases with microscopic or

macroscopic residual tumor. Among the 20 re-irradiations, all radiotherapies were performed with intensity-modulated radiotherapy (IMRT) technique, with the median dose of 60 Gy (40–70 Gy) and 60 Gy (50.4–63 Gy) for re-RT and SR + re-RT groups, respectively.

For systemic therapy, 3 cases (10.3%) received target therapy with Erbitux, and 20 cases (70.0%) received chemotherapy, including 8 concurrent with radiotherapy, 5 as adjuvant to either surgery or radiotherapy, and 7 receiving both. LRrNPCs that were diagnosed after the year of 2013 were more likely to receive chemotherapy for salvage treatment.

Overall outcomes and prognostic factors

After median follow-up of 36 months (range, 7–118 months), 12 locoregional progressions, 5 distal metastases, and 15 deaths were recorded. The LRPFS rates were 56.5% (95% CI: 45.6–67.4%) at 3-year and 38.7% (95% CI: 25.8–51.6%) at 5-year. The OS rates were 64.1% (95% CI: 54.9–73.3%) at 3-year and 54.3% (95% CI: 44.2–64.4%) at 5-year.

In univariate analysis, salvage treatments with SR, reRT, and SR + reRT all revealed superior LRPFS comparing to systemic treatment alone. Considering possible selection bias of rT stage among treatment groups, rT stage was included in multivariate analysis for adjustment. After adjusted for rT stage, the LRPFS advantage still presented in reRT group and SR + reRT group (reRT, HR: 0.06, P=0.009; SR + reRT, HR: 0.069, P=0.021). However, SR group failed to show a statistically significant LRPFS benefit (HR: 0.084, P=0.130) (*Table 2*). To exclude the STx group with a limited case number, further analysis was performed comparing LRPFS of SR, reRT, and SR + reRT groups. Nonetheless, no statistically significant difference was found (*Table 2*). For secondary endpoint, there was no significant difference in OS among treatment groups, chemotherapy use, recurrent stage, nor age groups found in this cohort.

Severe adverse events

Overall, 51.7% of the enrolled cases developed severe adverse events, including ORN in 34.5%, severe dysphagia in 20.7%, and temporal lobe necrosis in 6.9%. The distribution of severe complications among salvage modalities was provided in *Table 3*. Though there was no significant difference in the risk of severe complications among the 4 salvage treatment groups, cumulative EQD2 ≥130 Gy (RR: 9.0, P=0.013) over nasopharyngeal region was associated with higher risk of severe adverse events.

Grade 5 complications occurred in 2 (6.9%) cases, both underwent re-irradiation for rT2N0 recurrent NPCs. One suffered from nasal bleeding complicated with suffocation 8 months after re-irradiation. The other experienced hypovolemic shock due to nasal bleeding superimposing acquired-hemophilia, which developed 7 months after re-irradiation.

Discussion

In this preliminary analysis of treatment modalities, our study found superior LRPFS in re-irradiation and SR + re-RT subgroups when compared to systemic treatment alone, after adjustment for recurrent T stage (*Table 2*). Despite having possible negative confounding factors such as advanced rT stage and positive resection margins, the superiorities in LRPFS were still presented in the less favorable cases treated by reRT and SR + reRT (7,14). On the other hand, SR group, having more favorable population with all rT1-2 recurrences, failed to reach a statistically significant benefit over systemic treatment alone (*Table 2*, multivariate analysis). However, there was no significant difference in LRPFS when focusing on the 3 locoregionally-treated subgroups. Considering the limited case number in the STx group and discrepancy between the analytical results, further evaluation would be needed.

IMRT re-irradiation in LRrNPC

According to our finding, the role of re-irradiation was essential for recurrent NPC. The pooled 5-year local-failure-free survival of 72% was reported with great heterogeneity in a meta-analysis for re-irradiation of recurrent NPC (21). As recurrent T stage being a prognostic factor for local control, Leung *et al.* reported the 3-year local failure free survival of 66.7%, 66.7%, and 18.4% for rT1, rT2, and rT3 receiving salvage re-irradiation, respectively (25). However, there is limited literatures available for comparative outcomes between re-irradiation and other modalities, especially for advanced recurrent NPC.

In a retrospective propensity score-matched analysis, re-irradiation with IMRT technique revealed an inferior 5-year OS in selective rT1-3 NPC patients, comparing to endoscopic nasopharyngectomy (5-year OS: 55.5% *vs.* 77.1%, P=0.003) (18). Treatment complication-related

Table 2 Analysis for locoregional-progression-free survival

Factors	Univariate		Multivariate	
	Hazard ratio	P	Hazard ratio	P
rT[†]				
T1-2	Ref.	–	Ref.	–
T3-4	1.978	0.308	1.898	0.554
rN				
N0	Ref.	–	–	–
N+	1.648	0.420	–	–
Re-stage				
Stage I-II	Ref.	–	–	–
Stage III-IV	1.978	0.308	–	–
Salvage treatment				
STx	Ref.	–	Ref.	–
SR	0.044	0.010	0.084	0.130
reRT	0.055	0.006	0.060	0.009
SR + reRT	0.058	0.013	0.069	0.021
Salvage treatment*				
SR	Ref.	–	–	–
reRT	0.748	0.751	–	–
SR + reRT	0.935	0.927	–	–
Chemotherapy				
No	Ref.	–	–	–
Yes	1.964	0.321	–	–

[†], rT status was adjusted in multivariate analysis for selection bias; *, re-analysis of salvage treatment modalities excluding STx group.

Table 3 Severe complications based on salvage treatment modalities

Complications	SR (n=6)	ReRT (n=14)	SR + reRT (n=6)	STx (n=3)	P
Any ≥ grade 3 complications	33.3%	57.1%	66%	33.3%	0.605
ORN	16.7%	35.7%	50%	33.3%	0.355
Temporal necrosis	0%	14.3%	0%	0%	0.733
Severe dysphagia	16.7%	14.3%	33%	33.3%	0.884
Grade 5 complications	0%	14.3%	0%	0%	0.733

SR, surgical resection; ReRT, re-irradiation; ORN, osteoradionecrosis.

deaths occurred in 34.7% of the re-irradiation group having early recurrent NPCs. Grade 5 complications up to 35% was also reported in other re-irradiated cohorts (18,20,21,26). Yet, the enrolled cases of these studies exclusively received 2D conventional radiotherapy for their first NPC treatment courses. With the improvement of

Table 4 Published data suggesting constraints for critical organs in re-irradiation of LRrNPC

Literatures	Brainstem	Spinal cord	Temporal lobe	Optic chiasm	Optic nerve	Severe (≥ grade 3) late complication rate
Agas 2019 (27)	Dmax <81 Gy	Dmax <67.5 Gy	Dmax <90 Gy	Dmax <81 Gy	Dmax <81 Gy	23%
Chan 2017 (26)	D1% ≤78 Gy	D1cc ≤78 Gy	D1cc ≤84.5 Gy	78 Gy	78 Gy	73.3%
Qiu 2010 (28)	50 Gy*	40 Gy*	50 Gy*	54 Gy*	54 Gy*	36%

*, most of the dose constraints were given in the form of cumulative dose but the Qui 2010 were given for solely the re-irradiation plan.

technique, complication-related death has declined to 10% for the re-irradiated cases in our study, having IMRT as first radiotherapy in 72.4% of the cohort. Similarly, in another cohort having 60.5% of the first NPC treatment done by IMRT, grade 5 adverse event rate of re-irradiation was only 7.4% (26). With the popularity of IMRT in primary NPC treatment, fatal toxicity would be expected to decrease in salvage re-irradiation.

Despite the improvement in lethal toxicity with IMRT, high risk of ≥ grade 3 adverse events remains a major concern. Re-irradiation doses ranging from 40–70 Gy were still associated with severe complication rate up to 60% to 73.7% (20,21,26). Several dose constraints for critical organs in re-irradiation situations have been proposed (*Table 4*). While the salvage RT dose >60 Gy was reported to have better disease control (12), cumulative dose of EQD2 >130 Gy over nasopharyngeal region was associated with a 9 times higher risk for severe complications in our study. It seems that even with IMRT technique, adequate dose for oncological control still accompanied with the cost of high risk for developing severe complications and adverse effects on the quality of life (20,26).

Fractionated stereotactic radiotherapy (FSRT) was increasingly reported as an alternative modality for residual and recurrent NPC, having the 2-year local control rate of 55–82% with 10–49 Gy in 2–8 fractions (29). In a cohort study with median follow-up of 20.2 months, Wu *et al.* reported the late complication rate being 18.9% for 90 patients treated by FSRT (30). Seo *et al.* reported a 35 cases cohort treated by FSRT that the grade 4–5 complication rate was as low as 14.3% (31). With emerging evidences and longer follow-up, FSRT may become an important treatment option for residual and recurrent NPC in near future. Nevertheless, the optimal dose regimen and long-term result for late adverse event still warrant investigation at present.

Possible role of combining SR and re-irradiation in the modern era

In our study, combination of SR and re-irradiation was also an appropriate treatment option for recurrent NPC. With less destructive procedure and better visualization of surgical field, endoscopic surgery was increasingly used for locally advanced recurrent NPC in recent years (23,32,33). Weng *et al.* and Liu *et al.* have reported the complete resection rates of 91.6% and 90.1% in cohorts with 52.8% and 52.7% of rT3-4 NPC, respectively (23,32). When further stratified by rT stage, margin-free resections were achieved in 50–100% of rT3 and 53.8% rT4 recurrent NPC (33-35). No fatal surgical complication was recorded in previous nor this cohort (23,32,33). Regardless of these promising reports, all of the five rT3-4 cases receiving SR in our cohort had either involved margin or gross residual disease and therefore receiving adjuvant radiotherapy.

Comparative outcomes including that of combined modalities had been reported in five retrospective cohort studies as listed in *Table 5*. While two of them showed similar or worse outcomes, the other three revealed superior survival with combination of radiotherapy and SR. King *et al.* reported the mean disease-free survival (mDFS) of 55 months for recurrent NPC treated by combined modalities, which was even better than that of SR group achieving free surgical margins, having mDFS of 46.5 months (36). In a retrospective cohort study with 83.3% rT1-2 NPC, Na'ara *et al.* revealed that SR with additional adjuvant radiotherapy improved the 5-year OS and disease-specific survival (SR *vs.* SR + reRT, OS: 39% *vs.* 67%, P=0.05; DSS: 52% *vs.* 65%, P=0.048) (16). When comparing to salvage chemoradiotherapy, Weng *et al.* suggested a better survival outcome combining salvage surgery with adjuvant chemoradiotherapy (OS, HR: 0.468, P=0.043; DFS, HR: 0.393, P=0.008) (23). The benefit of combining surgery and chemoradiotherapy persisted in subgroup analysis for locally

Table 5 Published data for comparison between combining modalities and other treatments for recurrent nasopharyngeal cancer

Studies	Cohort	Reported results			Note
	No.	SR (no.)	Re-RT (no.)	SR + re-RT (no.)	
King, 2000 (36)	rT1-2: 29; rT3: 2	Mean OS: 18 m [7]; Mean DFS: 19 m [7]; Mean LRFS: 18m [7]	–	Mean OS: 60 m [23]; Mean DFS: 60 m [23]; Mean LRFS: 60 m [23]	OS, P=0.0024; DFS, P=0.0038; LRFS, P=0.01
Hsu, 2001 (13)	rT1-2: 28; rT3-4: 32	2Y OS: 56% [28] 2Y OS-RR: 1.13, P=0.81	–	2Y OS: 58% [29]	–
Chen, 2014* (37)	rT1-2: 28; rT3-4: 28; Sum: 67	5Y LRFS: 57.4% [19]; 5Y LRFS: 28.6% [7]; 5Y LRFS: 51% [33]; 5Y OS: 60.5% [33]	5Y LRFS: 53.3% [5]; 5Y LRFS: 38.5% [13]; 5Y LRFS: 31.7% [22]; 5Y OS: 48.7% [22]	5Y LRFS: 25% [4]; 5Y LRFS: 25% [8]; 5Y LRFS: 23.8% [12]; 5Y OS: 32.1% [12]	–
Na'ara, 2014 (16)	rT1-2: 645; rT3-4: 129; rN+: 11.3%	5Y OS: 39% [573]; 5Y DSS: 52% [573]; OS-HR: 1.2, P=0.04; DSS-HR: 1.18, P=0.04; DFS-HR: 1.6, P=0.05	–	5Y OS: 67% [190]; 5Y DSS: 65% [190]	–
Weng, 2017 (23)	rT1-2: 27; rT3-4: 33	–	Ref	OS, HR: 0.468, P=0.043; DFS, HR: 0.393, P=0.008	–

*, Chen 2014, only Stanford cohort was cited. The 5Y LRFS in the first line, second line, and last two lines were that of rT1-2, rT3-4, and overall cohort, respectively. SR, surgical resection; Re-RT, re-irradiation; 2Y/5Y, 2/5 years; OS, overall survival; DFS, disease-free survival; LRFS, locoregional-free survival; RR, risk ratio; HR, hazard ratio; Ref, reference for RR or HR.

advanced disease (23). In regard of adverse events, there was no significant additional hazard found for combined modalities in our study nor previous literatures (16,23). Further evaluation of the safety is warrant considering limited case number and possible selection bias in this study.

Strengths and limitations

With median follow-up of 3 years, this study compared local controls among SR, reRT, SR + reRT, and STx alone in LRrNPC. Having 83.3% of tumor resection done by endoscopic approach and IMRT accounted for 72.4% and 100% of the initial and salvage radiotherapy, our cohort could well reflect the clinical practice nowadays. The main limitations of this study included small sample size and retrospective design. The results were at risk of being underpowered to detect possible difference and affected by unadjusted confounders.

Conclusions

For LRrNPCs, locoregional treatments including reRT and SR + reRT may have local control advantage in comparison to systemic therapy alone, especially having the technical improvement with IMRT and endoscopic resection. Grade 5 complication of salvage re-irradiation would be expected to decrease with increasing use of IMRT in primary NPC treatment. Nonetheless, high incidence of severe complications was still a major concern. Larger cohort or prospective clinical trials are warrent to further evaluate the efficacy and safety of treatment modalities.

Acknowledgments

We appreciated the great dedication of the Head and Neck Cancer multidisciplinary team and all colleges from department of radiation oncology for thoughtful patient cares and inspiring discussions.
Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol had been registered and verified by the institutional review board (VGHKS18-CT11-11). Informed consent was waived due to the retrospective nature of the study.

References

1. Yu MC, Yuan JM. epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 2002;12:421-9.
2. Mahdavifar N, Ghoncheh M, Mohammadian-Hafshejani A, et al. Epidemiology and Inequality in the Incidence and Mortality of Nasopharynx Cancer in Asia. Osong Public Health Res Perspect 2016;7:360-72.
3. Mahdavifar N, Towhidi F, Makhsosi BR, et al. Incidence and Mortality of Nasopharynx Cancer and Its Relationship With Human Development Index in the World in 2012. World J Oncol 2016;7:109-18.
4. Sun X, Su S, Chen C, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. Radiother Oncol 2014;110:398-403.
5. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310-7.
6. Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol 2015;16:645-55.
7. Suárez C, Rodrigo JP, Rinaldo A, et al. Current treatment options for recurrent nasopharyngeal cancer. Eur Arch Otorhinolaryngol 2010;267:1811-24.
8. Xu T, Tang J, Gu M, et al. Recurrent nasopharyngeal carcinoma: a clinical dilemma and challenge. Curr Oncol 2013;20:e406-19.
9. Roeder F, Zwicker F, Saleh-Ebrahimi L, et al. Intensity modulated or fractionated sterotatic re-irradiation in patients with recurrent nasopharyngeal cancer. Radiat Oncol 2011. doi: https://doi.org/10.1186/1748-717X-6-22
10. Koutcher L, Lee N, Zelefsky M, et al. Reirradiation of locally recurrent nasopharynx cancer with external beam radiotherapy with or without brachytherapy. Int J Radiat Oncol Biol Phys 2010;76:130-7.
11. Hao SP, Tsang NM. Surgical Management of Recurrent nasopharyngeal carcinoma. Chang Gung Med J 2010;33:361-9.
12. Teo PM, Kwan WH, Chan AT, et al. How Successful Is High-Dose (≥60 GY) Reirradiation Using Mainly External Beams in Salvaging Local Failures of Nasopharyngeal Carcinoma? Int J Radiat Oncol Biol Phys 1998;40:897-913.
13. Hsu MM, Hong RL, Ting LL, et al. Factors Affecting the Overall Survival After Salvage Surgery in Patients With Recurrent Nasopharyngeal Carcinoma at the Primary Site. Arch Otolaryngol Head Neck Surg 2001;127:798-802.
14. Hao SP, Tsang NM, Chang KP, et al. Nasopharyngectomy for recurrent nasopharyngeal carcinoma: a review of 53 patients and prognostic factors. Acta Otolaryngol 2008;128:473-81.
15. Poon D, Yap SP, Wong ZW, et al. Concurrent chemoradiotherapy in locoregionally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2004;59:1312-8.
16. Na'ara S, Amit M, Billan S, et al. Outcome of patients undergoing salvage surgery for recurrent nasopharyngeal carcinoma: a meta-analysis. Ann Surg Oncol 2014;21:3056-62.
17. Yue Q, Zhang M, Chen Y, et al. Establishment of prognostic factors in recurrent nasopharyngeal carcinoma patients who received salvage intensity-modulated radiotherapy: A meta-analysis. Oral Oncol 2018;81:81-8.
18. You R, Zou X, Hua YJ, et al. Salvage endoscopic nasopharyngectomy is superior to intensity-modulated radiation therapy for local recurrence of selected T1-T3 nasopharyngeal carcinoma - A case-matched comparison. Radiother Oncol 2015;115:399-406.
19. Emanuelli E, Albu S, Cazzador D, et al. Endoscopic surgery for recurrent undifferentiated nasopharyngeal carcinoma. J Craniofac Surg 2014;25:1003-8.
20. Tian YM, Huang WZ, Yuan X, et al. The challenge in treating locally recurrent T3-4 nasopharyngeal carcinoma: the survival benefit and severe late toxicities

of re-irradiation with intensity-modulated radiotherapy. Oncotarget 2017;8:43450-7.
21. Leong YH, Soon YY, Lee KM, et al. Long-term outcomes after reirradiation in nasopharyngeal carcinoma with intensity-modulated radiotherapy: A meta-analysis. Head Neck 2018;40:622-31.
22. Liu LT, Chen QY, Tang LQ, et al. With or without reirradiation in advanced local recurrent nasopharyngeal carcinoma: a case-control study. BMC Cancer 2016;16:774.
23. Weng J, Wei J, Si J, et al. Clinical outcomes of residual or recurrent nasopharyngeal carcinoma treated with endoscopic nasopharyngectomy plus chemoradiotherapy or with chemoradiotherapy alone: a retrospective study. PeerJ 2017;5:e3912.
24. Bursac Z, Gauss CH, Williams DK, et al. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008;3:17.
25. Leung TW, Tung SY, Sze WK, et al. Salvage radiation therapy for locally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2000;48:1331-8.
26. Chan OS, Sze HC, Lee MC, et al. Reirradiation with intensity-modulated radiotherapy for locally recurrent T3 to T4 nasopharyngeal carcinoma. Head Neck 2017;39:533-40.
27. Agas RA, Yu KK, Sogono PG, et al. Reirradiation for Recurrent Nasopharyngeal Carcinomas: Experience From an Academic Tertiary Center in a Low- to Middle-Income Country. J Glob Oncol 2019;5:1-14.
28. Qiu S, Lin S, Tham IW, et al. Intensity-modulated radiation therapy in the salvage of locally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2012;83:676-83.
29. Lee VH, Kwong DL, Leung TW, et al. Hyperfractionation compared to standard fractionation in intensity-modulated radiation therapy for patients with locally advanced recurrent nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol 2017;274:1067-78.
30. Wu SX, Chua DT, Deng ML, et al. Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2007;69:761-9.
31. Seo Y, Yoo H, Yoo S, et al. Robotic system-based fractionated stereotactic radiotherapy in locally recurrent nasopharyngeal carcinoma. Radiother Oncol 2009;93:570-4.
32. 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;22:834-42.
33. Wong EH, Liew YT, Abu Bakar MZ, et al. A preliminary report on the role of endoscopic endonasal nasopharyngectomy in recurrent rT3 and rT4 nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol 2017;274:275-81.
34. Ho AS, Kaplan MJ, Fee WE Jr, et al. Targeted endoscopic salvage nasopharyngectomy for recurrent nasopharyngeal carcinoma. Int Forum Allergy Rhinol 2012;2:166-73.
35. Hsu NI, Shen PH, Chao SS, et al. En bloc resection concept for endoscopic endonasal nasopharyngectomy: surgical anatomy and outcome. Chin Med J (Engl) 2014;127:2934-9.
36. King WW, Ku PK, Mok CO, et al. Nasopharyngectomy in the treatment of recurrent nasopharyngeal carcinoma: a twelve-year experience. Head Neck 2000;22:215-22.
37. Chen C, Fee W, Chen J, et al. Salvage treatment for locally recurrent nasopharyngeal carcinoma (NPC). Am J Clin Oncol 2014;37:327-31.

doi: 10.21037/tro.2019.07.02
Cite this article as: Chien JC, Huang CY, Hu YC, Chang KC, Chang KP, Kang BH, Liu WS. The treatment modalities and outcomes of recurrent nasopharyngeal carcinoma: a retrospective cohort study in the modern era. Ther Radiol Oncol 2019;3:25.