Translational Oncology 13 (2020) 100765

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Comparing Long-Term Survival and Late Toxicities of Different Sequential Chemotherapy Regimens with Intensity-Modulated Radiotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma

Mingyao Wu, Dan Ou, Chaosu Hu, Xiayun He *

Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
Department of Oncology, Shanghai Medical College, Shanghai, China

ARTICLE INFO

Article history:
Received 18 February 2020
Received in revised form 15 March 2020
Accepted 16 March 2020
Available online xxxx

ABSTRACT

OBJECTIVES: To evaluate long-term survival outcomes and late toxicities of the sequential chemotherapy regimen of gemcitabine plus cisplatin (GP) compared with cisplatin plus fluorouracil (PF) in locoregionally advanced nasopharyngeal carcinoma (NPC). *MATERIALS AND METHODS:* From June 2005 to December 2014, 235 patients with pathologically confirmed NPC treated with intensity-modulated radiotherapy (IMRT) combined with GP (n = 144) or PF (n = 91) were retrospectively analyzed. *RESULTS:* After a median follow-up of 61 months, the 5-year overall survival (OS) rates were not significantly different between GP and PF groups (84.2% vs. 74.4%, $P = .208$). The 5-year local control rates were significantly improved in the GP group (96.3% vs 84.1%, $P = .010$). Subgroup analysis demonstrated that the increased benefits of GP were from T1-3 classification (99% vs. 87.8%, $P = .013$) and stage III patients (100% vs. 82.4%, $P = .017$). The most common late adverse events were xerostomia and hearing impairment. The incidences of grade 3 to 4 late toxicities were relatively low and were similar in the two groups. *CONCLUSIONS:* Sequential chemotherapy combined with IMRT achieved satisfactory survival outcomes in locoregionally advanced NPC with acceptable late toxicities. The GP regimen significantly improved local control compared with PF regimen. Further phase III randomized clinical studies were warranted.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant neoplasm with high radiosensitivity, which has unique mode of geographic and epidemiologic distributions. Because of the special anatomical location of the tumor, radiotherapy (RT) plays an essential role in the treatment of non-metastatic NPC. Approximately 70% of newly diagnosed nasopharyngeal carcinoma cases are classified as locoregionally advanced disease. The approach combining chemotherapy with radiotherapy is the cornerstone of the management in patients with locoregionally advanced NPC. Concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy has been deemed the standard treatment for locally advanced NPC for years [1]. In the recent update of the MAC-NPC meta-analysis, the value of the CCRT on survival benefits was confirmed in locoregionally advanced NPC patients [2]. However, the tolerance of concurrent chemotherapy was unsatisfied due to the high incidence of acute toxicity. A meta-analysis conducted by Du and his colleagues found that the incidences of severe late toxicities were higher in NPC patients who received CCRT [3]. In recent years, with the development of radiation technology which achieves high-dose coverage of target volume, distant metastasis has substituted the local and regional recurrence for the main failure pattern in locoregionally advanced NPC [4–6]. CCRT may not be adequate for patients at high risk of distant failure in the intensity-modulated radiotherapy (IMRT) era. Hence, more potent systemic therapy needs to be investigated with the goal of reducing distant metastasis.

The addition of induction chemotherapy (IC) or adjuvant chemotherapy (AC) to radiotherapy might reduce distant metastasis in patients with high-risk of metastasis. A meta-analysis by OuYang et al. found that IC significantly improved distant control and obtained an absolute overall survival (OS) benefit of 5.13% at 3 years [7]. Recently, IC has been often used in clinical practice for locoregionally advanced NPC, especially in endemic areas with plenty of patients waiting for RT. Liu et al. reported long-term outcomes of a consecutive cohort of 256 NPC patients receiving either IC-RT or CCRT. The results showed that compared with CCRT, IC-RT obtained similar long-term survivals but significantly reduced severe acute toxicities (grade 3-4) [8]. Sequential chemotherapy combined with RT might be an attractive alternative option in NPC. Until the appearance of some new drugs such as the taxanes and gemcitabine, the regimen combining

* Address all correspondence to: Xiayun He, Dongan Road 270, Fudan University Shanghai Cancer Center, Shanghai, China.
E-mail address: donganlu270hao@gmail.com. (X. He).

http://dx.doi.org/10.1016/j.tranon.2020.100765

cisplatin with fluorouracil (PF) has been generally considered as the standard protocol for IC/AC and extensively applied to locoregionally advanced NPC. Gemcitabine is a novel drug with impressive anticancer activities. The results of some studies indicate that gemcitabine is an effective drug for the treatment of NPC when used prior to definitive radiotherapy [9,10]. To compare the efficacy and toxicity of the chemotherapy regimens of PF with gemcitabine and cisplatin (GP) sequentially combined with IMRT in locoregionally NPC, we retrospectively analyzed the outcomes of patients who received these two different regimens in our institution.

Methods

Patients

The current retrospective study reviewed the patients with pathologically confirmed non-metastatic NPC treated definitively with IMRT from June 2005 to December 2014. All patients were staged according to the 7th Edition of American Joint Committee on Cancer (AJCC) staging system. Initial evaluations included clinical examination, blood biochemical index, nasopharyngoscopy, enhanced magnetic resonance imaging (MRI) of the nasopharynx and neck. For the exclusion of metastasis, chest X-ray/computed tomography (CT), abdominal ultrasound/CT and bone emission computed tomography (ECT) were performed. Other tests were required if clinically indicated. Dental extraction was performed before radiotherapy when necessary. Approval for this study was acquired from the Institutional Review Board. Prior to treatment, informed written consent was obtained from each patient.

Radiotherapy

Radiotherapy techniques have been previously described [11]. According to T classification, the prescription dose to primary tumor was distinct (T1-2: 66 Gy/30 fractions, T3-4: 70.4 Gy/32 fractions). The total dose to metastatic lymph node was 66Gy in 30 to 32 fractions. PTV60 which defined as the high-risk clinical target volume (CTV) plus a 0.5 cm margin was prescribed 60 Gy/30 to 32 fractions. PTV54 was prescribed 54 Gy/30 to 32 fractions for the low-risk CTV plus a 0.5 cm margin. All patients received irradiation 5 days per week, one fraction daily.

Chemotherapy

In this study all patients received sequential chemotherapy combined with IMRT. In the PF group, patients received 2 cycles of induction chemotherapy: cisplatin 25 mg/m^2 days 1 to 3, and 5-Fu 2500 mg/m^2 as an intravenous infusion over 120 hours, every 21 days. Four weeks after the completion of IMRT, two courses of AC with the preceding regimen were administered every 3 weeks. In the GP group, patients were also treated with two courses of IC and AC, respectively: gemcitabine (1000 mg/m^2) administered intravenously for 30 minutes on days 1 and 8, and cisplatin (25 mg/m^2) infusion on days 1 to 3, repeated every 3 weeks.

Chemotherapy was postponed if the hematologic parameters of patients were disqualified. Furthermore, the dose of the next cycles would be reduced by 20% in case of grade 4 hematological toxicity. Blood routine and blood biochemical parameters were examined before each chemotherapy cycle.

Follow-Up

Patients were assessed weekly during radiotherapy. After completion of treatment, participants were followed up every 3 months in the first 2 years, every 6 months for 3 to 5 years and annually after 5 years. Physical examination, nasopharyngoscopy and imaging assessments were detailed in our previous study [12]. Late radiotherapy-related toxicities were graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research on Treatment of Cancer (EORTC) late radiation morbidity scoring schema.

Statistics

Chi-square test or Fisher exact test for categorical variables were performed in the baseline comparison, and Student's *t* test for continuous variables. The local control, regional control, distant metastasis-free survival (DMFS) and overall survival (OS) rates were estimated by Kaplan-Meier method. The times to local or regional recurrence and distant metastases were calculated between the start of treatment and the dates of local or regional relapse and distant failure, respectively. Survival differences between groups were calculated with log-rank tests. Univariate analysis (UVA) was performed using a Cox proportional hazards model. Factors with a P value $<.25$ in UVA were included in a multivariate Cox model. Statistical analyses were performed with SPSS software, version 20 (IBM, Armonk, NY, USA). A two-sided $P < .05$ was considered statistically significant.

Results

Patients

Between June 2005 and December 2014, a total of 235 consecutive patients with newly diagnosed locoregionally advanced NPC treated definitively with IMRT were analyzed. The baseline clinical and demographic characteristics of patients are listed in Table 1. More male patients were in GP group ($P = .038$) and patients receiving PF chemotherapy had worse performance status ($P < .001$).

Treatment Compliance

In the PF group (n = 91), 87 (95.6%) patients completed two cycles of induction chemotherapy. The reasons for the remaining four patients completing only one course were liver function damage (n = 2), severe myelosuppression (n = 1) and pneumonia (n = 1). In the GP group (n = 144), 141(97.9%) patients completed two cycles of IC, and 3 patients discontinued this regime after one cycle, two because of skin reaction (grade 3) and one because of liver function damage (grade 2). All the patients completed radical radiotherapy. Sixty-eight (74.7%) patients in the PF group and 132 (91.7%) patients in the GP group received adjuvant chemotherapy after IMRT. For both groups, the most common reasons of patients not administered adjuvant chemotherapy were myelosuppression and patients' refusal.

Table 1
Patient characteristics

Characteristics	PF group (n = 91) n (%)	GP group (n = 144) n (%)	*P*
Age (Years)			
Median	52.4	48.8	.019
Gender			.038
Male	61 (67)	114 (79.2)	
Female	30 (33)	30 (20.8)	
KP score			<.001
70	19 (20.9)	7 (4.9)	
80	50 (54.9)	65 (45.1)	
90	22 (24.2)	72 (50)	
T stage			.082
T1	3 (3.3)	18 (12.5)	
T2	34 (37.4)	49 (34)	
T3	30 (33)	49 (34)	
T4	24 (26.4)	28 (19.5)	
N stage			.173
N0	5 (5.5)	14 (9.7)	
N1	38 (41.8)	41 (28.5)	
N2	31 (34.1)	59 (41.0)	
N3	17 (18.7)	30 (20.8)	
Overall stage			.515
II*	16 (17.6)	22 (15.3)	
III	36 (39.6)	68 (47.2)	
IV	39 (42.9)	54 (37.5)	

* Stage II with lymph node measured 4 cm or more in diameter.

Table 2
Treatment failure patterns of NPC patients in the PF group and GP group

Failure pattern	PF group (n = 91) n (%)	GP group (n = 144) n (%)	*P*
Local recurrence			.039
Yes	13 (14.3%)	9 (6.3%)	
No	78 (85.7%)	135 (93.8%)	
Regional recurrence			.450
Yes	11 (12.1%)	13 (9%)	
No	80 (87.9%)	131 (91%)	
Distant metastases			.579
Yes	13 (14.3%)	17 (11.8%)	
No	78 (85.7%)	127 (88.2%)	

Treatment Failures and Survivals

For the whole population, the median follow-up time was 61 (range, 8-123) months. Median follow-up times for PF and GP groups were 45 (range, 10-123) months and 67 (range, 8-117) months, respectively. The failure patterns of treatment for the PF and GP groups were shown in Table 2. Comparing the two groups, no significant differences were found for the incidences of regional recurrence (P = .450) and distant metastases (P = .579). However, more patients developed local recurrence in the PF group (14.3% vs. 6.3%, P = .039).

At the latest follow-up, 39 patients died (PF: n = 16; GP: n = 23) and 168 patients (PF: n = 63; GP: n = 105) were alive and disease free. The 5-year OS, local control, regional control and DMFS rates for all patients were 81.3%, 91.7%, 90.5% and 87.0%, respectively. The 5-year local control rates were significantly different between PF and GP groups (84.1% vs. 96.3%, P = .010). Meanwhile, the 5-year regional control, DMFS and OS rates were not significantly different between PF and GP groups (regional control rates, 86.9% vs. 92.7%, P = .273; DMFS rates, 81.3% vs. 89.2%, P = .351; OS, 74.4% vs. 84.2%, P = .208) (Figure 1).

Prognostic Factors

The parameters included in the multivariate analysis (MVA) were gender (female vs. male), age (≤50 years vs. >50 years), T classification (T4 vs. T1-3), N classification (N2-3 vs. N0-N1) and chemotherapy regimen (GP vs. PF). OS was independently correlated with gender, T classification and N classification. Regional control rates and DMFS rates were correlated with N classification only. T classification and chemotherapy regimen independently correlated with local control rates (HR = 3.599, 95%CI, 1.540-8.411, P = .003 and HR = 0.628, 95%CI, 0.406-0.972, P = .037, respectively) (Table 3). Further subgroup analysis indicated that stage III and relatively early T stage (T1-3) patients who received GP chemotherapy obtained significantly higher local control rates (P = .017 for stage III; P = .013 for T1-3, respectively). There was a tendency of enhancement for the local control rates in stage IV patients receiving GP chemotherapy regimen (89.6% vs. 78.3%, P = .099) (Figure 2).

Late Toxicities

The late RT toxicities were recorded in accordance with the RTOG late radiation morbidity scoring method. The type and frequency of late toxicities were summarized in Table 4. Overall, xerostomia and hearing impairment were the most common late toxicities in both groups. No significant differences of late toxicities were observed between the two groups. The incidences of severe late adverse effects were relatively low, which mainly included cranial nerve palsy (PF: 1 case; GP: 4 cases), trismus (PF: 2 case; GP: 5 cases) and grade 3 hearing impairment (PF: 1 case; GP: 3 cases).

Discussion

In this study, we retrospectively compared two sequential chemotherapy regimens (PF vs. GP) combined with IMRT in locoregionally advanced NPC. With a median follow-up of 61 months, the 5-year regional control,

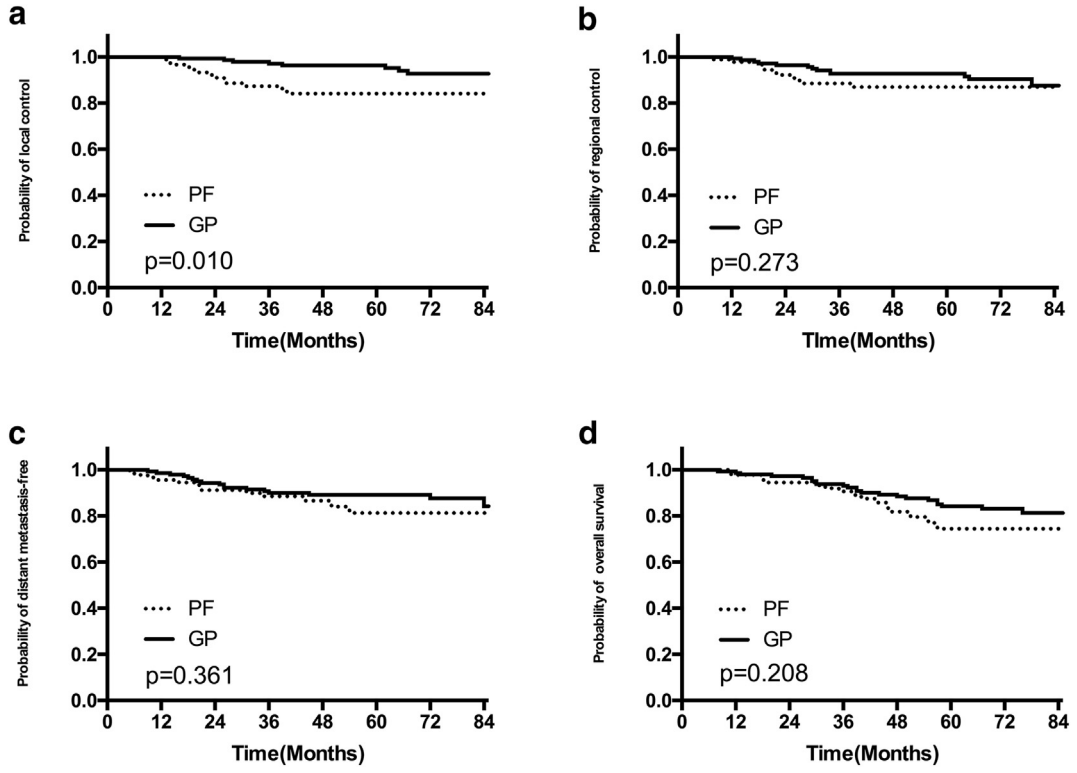

Figure 1. Kaplan-Meier estimates of survival curves for the two treatment arms. a: local control, b: regional control, c: distant metastasis-free survival, d: overall survival comparing patients treated by GP or PF chemotherapy.

Table 3
Multivariate analysis of potential prognostic factors for OS, local control, regional control and DMFS rates

	Factors	HR(95%CI)	*P*
OS	Age: >50y vs ≤50y	3.297(1.612-6.745)	.001
	T classification: T4 vs T1-3	2.733(1.438-5.194)	.002
	N classification: N2-3 vs N0-N1	4.089(1.850-9.039)	.001
	Chemotherapy regimen: GP vs PF	0.893(0.644-1.239)	.498
Local control	Age: >50y vs ≤50y	1.824(0.722-4.607)	.204
	T classification: T4 vs T1-3	3.599(1.540-8.411)	.003
	Chemotherapy regimen: GP vs PF	0.628(0.406-0.972)	.037
Regional control	Age: >50y vs ≤50y	2.201(0.952-5.089)	.065
	N classification: N2-3 vs N0-N1	4.313(1.462-12.719)	.008
DMFS	Sex: female vs male	0.454(0.157-1.310)	.144
	Age: >50y vs ≤50y	1.756(0.834-3.698)	.138
	N classification: N2-3 vs N0-N1	4.326(1.644-11.385)	.003

HR: hazard ratio; CI: confidence interval.

DMFS and OS rates for the whole cohort were 90.5%, 87.0% and 81.3%, respectively. The results showed no statistical differences between the regional control, DMFS, and OS rates of these two treatment groups. For all patients, the 5-year local control rate was 91.7%. Moreover, significant improvement in favor of GP regimen was found for local control (96.3% vs. 84.1%, $P = .010$). Further subgroup analysis demonstrated that GP combined with IMRT exhibited a lower local failure rate in the subgroups of patients with T1-3 classification or stage III diseases ($P = .013$ and $P = .017$, respectively).

In the MVA for OS, advanced T classification, N classification and elder age were independently correlated with decreased OS. Similarly, Wu et al. retrospectively reported the 10-year survival outcomes for 614 consecutive NPC patients who treated with IMRT. In their multivariate analysis, the risk factors for poor OS were advanced T classification, N classification and elder age as well [6].

Due to the chemo-sensitive characteristic of NPC, chemotherapy occupies a crucial position in the definitive treatment of advanced NPC. For decades, the platinum-based doublet chemotherapy (PF) served as the most commonly used regimen for locoregionally advanced NPC. In a prospective multicenter study, 316 NPC patients confirmed by pathology were randomly assigned to two groups. One group underwent radiotherapy alone and the other received concurrent chemoradiotherapy followed by adjuvant PF chemotherapy. The results demonstrated survival benefits in patients who received the regimen of concurrent chemotherapy plus adjuvant PF [13]. However, the majority of previous studies were based on two-dimensional radiotherapy. With the optimization of dosage, the advanced radiotherapy technique IMRT has been widely used. Excellent local-regional control for NPC was achieved with this progressive technique, while unsatisfactory distant control ultimately succumbed to the disease [14,15]. Since the distant metastasis was not decreased obviously in the IMRT era, more attention has been focused on the exploration of systemic therapies dealing with distant metastasis.

Over the years, the application of some novel drugs in NPC such as docetaxel and gemcitabine has sparked strong interest. Gemcitabine is a nucleoside analog, which works by inhibiting DNA synthesis. The synergistic effects of gemcitabine and cisplatin observed in vitro have laid the foundation for its subsequent clinical application [16]. Several researches demonstrated that encouraging efficacy results have been obtained with tolerable toxicity profiles while using regimens containing gemcitabine in metastatic and recurrent NPC patients [17,18]. Zhang et al. conducted the first randomized multicenter trial comparing the therapeutic and side effects of GP versus PF in recurrent or metastatic NPC. They reported that patients receiving GP chemotherapy achieved a significant prolongation of median progression-free survival compared with those in the PF group (7.0 months vs. 5.6 months, $P < .0001$) [18]. Due to its superior effectiveness, GP regimen has been changed from a category 2A to a category 1 recommendation for recurrent or metastatic NPC in the updated National Comprehensive Cancer Network (NCCN) guidelines. Regarding

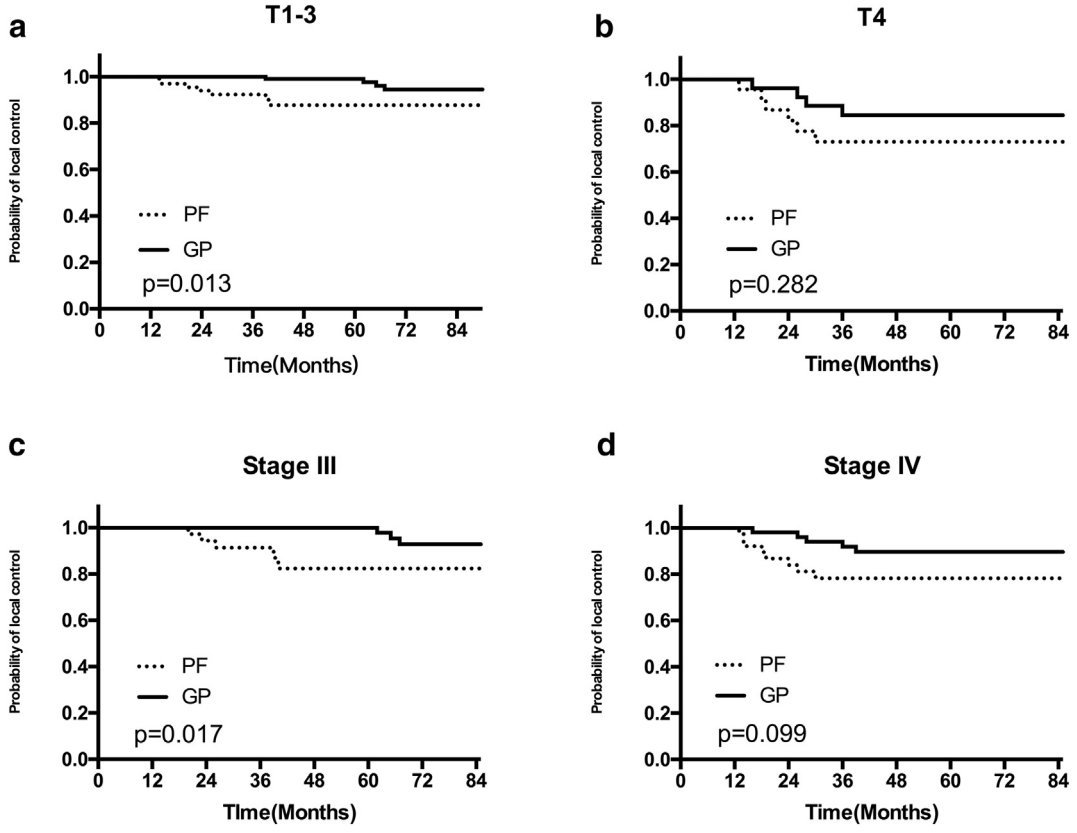

Figure 2. Kaplan-Meier curves of local control according to treatment groups in different sub-groups. a: T1-3, b: T4, c: stage III, d: stage IV.

Table 4
Late toxicities

Toxicities	PF group (n = 91)	GP group (n = 144)	*P*
	n (%)	n (%)	
Neck fibrosis	27 (29.7%)	47 (32.6%)	.633
Xerostomia	50 (54.9%)	88 (61.1%)	.350
Trismus	2 (2.2%)	5 (3.5%)	.710
Dysphagia	0 (0%)	0 (0%)	N/A
Hearing impairment	40 (44.0%)	66 (45.8%)	.778
Temporal necrosis	0 (0%)	0 (0%)	N/A
Cranial nerve palsy	1 (1.1%)	4 (2.8%)	.651

the costs and survival outcomes, Chen et al. conducted a Markov model to compare the cost-effectiveness of two cisplatin-based chemotherapy regimens (GP and PF) and found GP regimen was a superior alternative for recurrent or metastatic NPC patients [19]. Moreover, recent studies have also shown that gemcitabine-containing regimens are effective in patients with locoregionally advanced NPC, with tolerable toxicity profiles [20–22]. A retrospective study from Fujian Provincial Cancer Hospital analyzed 604 patients with locoregionally advanced NPC. The results demonstrated that patients receiving GP had significantly higher OS compared with PF ($P = .038$) and had a trend toward improved DMFS ($P = .109$). Patients receiving TP regimen (taxol + cisplatin) only had improved DMFS ($P = .038$). GP regimen may be more effective than TP/PF regimen for treating locoregionally advanced NPC [23]. In our study, GP group achieved a significantly higher 5-year local control rates compared with PF group (96.3% vs. 84.1%, $P = .010$). Several randomized trials are also evaluating the treatment benefits of utilizing GP regimen combined with IMRT in locoregionally advanced NPC (e.g. NCT01854203 and NCT03366415), and the value of such strategies is expected to be confirmed.

While the therapeutic outcome of NPC patients have significantly improved with the development of radiotherapy technology (e.g. IMRT) and broader incorporation of chemotherapy with RT [24–26], more and more attention was paid to treatment-related late toxicities [27,28]. Compared with 2D or 3DRT, IMRT was related to less severe physician-assessed late toxicities and improved patient-reported quality of life [29]. In a retrospective study of 3328 patients with NPC from 6 individual oncology centers in Hong Kong, a small number of patients had late adverse reactions as follows: hearing loss requiring hearing aids (7.1%), cranial nerve palsies (5.1%), dysphagia requiring tube feeding for a long period (3%), and symptomatic temporal lobe necrosis (0.9%) [14]. A recent published meta-analysis aimed to evaluate the efficacy and side effects of two chemotherapy regimens (GP vs. PF) indicated that the GP chemotherapy was superior to the PF chemotherapy, in terms of 1-year and 3-year survival rates. On the other hand, there was no significant difference in adverse reactions between the two regimens [30]. In our cohort, no treatment-related deaths were observed. The late toxicities were all mild in both groups, among which xerostomia and hearing impairment occurred most frequently. No significant differences in late toxicities were observed between these two regimen groups.

Conclusion

In conclusion, compared with the PF regimen, the GP regimen combined with IMRT provided satisfactory survival benefits for locoregionally advanced NPC, especially excellent local control rates. With long-term follow-up, there were no differences in late adverse toxicities between the two groups. The results of ongoing randomized trials concerning GP chemotherapy for locoregionally advanced NPC are being awaited.

Acknowledgements

We are grateful for the support of the Department of Radiation Oncology. The views expressed in this publication are those of the authors.

Funding Sources

This work was supported by the Shanghai Anticancer Association EYAS PROJECT (grant no: SACA-CY1A02) and institutional grant of Fudan University Shanghai Cancer Center (grant no: YJ201703).

Conflict of Interest

No conflicts of interest to disclose.

References

[1] Y.P. Chen, A.T.C. Chan, Q.T. Le, et al., Nasopharyngeal carcinoma, Lancet 394 (10192) (2019) 64–80.
[2] P. Blanchard, A. Lee, S. Marguet, et al., Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis, Lancet Oncol 16 (6) (2015) 645–655.
[3] C.R. Du, H.M. Ying, F.F. Kong, et al., Concurrent chemoradiotherapy was associated with a higher severe late toxicity rate in nasopharyngeal carcinoma patients compared with radiotherapy alone: a meta-analysis based on randomized controlled trials, Radiat Oncol 10 (2015) 70.
[4] X. Ou, X. Zhou, Q. Shi, et al., Treatment outcomes and late toxicities of 869 patients with nasopharyngeal carcinoma treated with definitive intensity modulated radiation therapy: new insight into the value of total dose of cisplatin and radiation boost, Oncotarget 6 (35) (2015) 38381–38397.
[5] X. Sun, S. Su, C. Chen, et al., Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities, Radiother Oncol 110 (3) (2014) 398–403.
[6] L.R. Wu, Y.T. Liu, N. Jiang, et al., Ten-year survival outcomes for patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy: An analysis of 614 patients from a single center, Oral Oncol 69 (2017) 26–32.
[7] P.Y. OuYang, C. Xie, Y.P. Mao, et al., Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials, Ann Oncol 24 (8) (2013) 2136–2146.
[8] Y.C. Liu, W.Y. Wang, C.W. Twu, et al., Comparison long-term outcome of definitive radiotherapy plus different chemotherapy schedules in patients with advanced nasopharyngeal carcinoma, Sci Rep 8 (1) (2018) 470.
[9] W. Tan, E. Tan, D. Lim, et al., Advances in systemic treatment for nasopharyngeal carcinoma, Chin Clin Oncol 5 (2) (2016) 21.
[10] W. Fangzheng, S. Quanquan, J. Chuner, et al., Gemcitabine/cisplatin induction chemotherapy before concurrent chemotherapy and intensity-modulated radiotherapy improves outcomes for locoregionally advanced nasopharyngeal carcinoma, Oncotarget 8 (57) (2017) 96798–96808.
[11] M. Wu, D. Ou, X. He, et al., Long-term results of a phase II study of gemcitabine and cisplatin chemotherapy combined with intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma, Oral Oncol 73 (2017) 118–123.
[12] M.Y. Wu, X.Y. He, C.S. Hu, Tumor regression and patterns of distant metastasis of T1-T2 nasopharyngeal carcinoma with intensity-modulated radiotherapy, PLoS One 11 (4) (2016), e0154501.
[13] Y. Chen, Y. Sun, S.B. Liang, et al., Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVB nasopharyngeal carcinoma from endemic regions of China, Cancer 119 (12) (2013) 2230–2238.
[14] K.H. Au, R.K.C. Ngan, A.W.Y. Ng, et al., Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: A report of 3328 patients (HKNPCSG 1301 study), Oral Oncol 77 (2018) 16–21.
[15] X.S. Sun, S.L. Liu, M.J. Luo, et al., The association between the development of radiation therapy, image technology, and chemotherapy, and the survival of patients with nasopharyngeal carcinoma: A cohort study from 1990 to 2012, Int J Radiat Oncol Biol Phys 105 (3) (2019) 581–590.
[16] A.M. Bergman, V.W. Ruiz van Haperen, G. Veerman, et al., Synergistic interaction between cisplatin and gemcitabine in vitro, Clin Cancer Res 2 (3) (1996) 521–530.
[17] Y. Jin, Y.X. Shi, X.Y. Cai, et al., Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma, J Cancer Res Clin Oncol 138 (10) (2012) 1717–1725.
[18] L. Zhang, Y. Huang, S. Hong, et al., Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial, Lancet 388 (10054) (2016) 1883–1892.
[19] X. Chen, W. Liang, N. Wan, et al., Cost-effectiveness analysis of gemcitabine plus cisplatin versus fluorouracil plus cisplatin for first-line treatment of recurrent or metastatic nasopharyngeal carcinoma, Oral Oncol 94 (2019) 80–85.
[20] M.F. Gu, L.Z. Liu, L.J. He, et al., Sequential chemoradiotherapy with gemcitabine and cisplatin for locoregionally advanced nasopharyngeal carcinoma, Int J Cancer 132 (1) (2013) 215–223.
[21] W. Zheng, S. Qiu, L. Huang, et al., Is gemcitabine and cisplatin induction chemotherapy superior in locoregionally advanced nasopharyngeal carcinoma? Pak J Med Sci 31 (4) (2015) 781–786.
[22] Y. Zhang, L. Chen, G.Q. Hu, et al., Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma, N Engl J Med 381 (12) (2019) 1124–1135.
[23] L. Zhao, M. Xu, W. Jiang, et al., Induction chemotherapy for the treatment of non-endemic locally advanced nasopharyngeal carcinoma, Oncotarget 8 (4) (2017) 6763–6774.

[24] T. Xu, X. Zhou, C. Shen, et al., Suggestions for surveillance and radiation strategy in nasopharyngeal carcinoma treated with IMRT: Based on hazard-rate and patterns of recurrence, Oral Oncol 76 (2018) 61–67.
[25] H. Yang, X. Chen, S. Lin, et al., Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: A prospective, multi-center, randomized clinical trial, Radiother Oncol 126 (1) (2018) 37–42.
[26] M.X. Zhang, J. Li, G.P. Shen, et al., Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up, Eur J Cancer 51 (17) (2015) 2587–2595.
[27] L. Zeng, Y.M. Tian, X.M. Sun, et al., Late toxicities after intensity-modulated radiotherapy for nasopharyngeal carcinoma: patient and treatment-related risk factors, Br J Cancer 110 (1) (2014) 49–54.
[28] J.W. Chan, U. Parvathaneni, S.S. Yom, Reducing radiation-related morbidity in the treatment of nasopharyngeal carcinoma, Future Oncol 13 (5) (2017) 425–431.
[29] T.L. Huang, C.Y. Chien, W.L. Tsai, et al., Long-term late toxicities and quality of life for survivors of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy versus non-intensity-modulated radiotherapy, Head Neck 38 (Suppl. 1) (2016) E1026–E1032.
[30] Q. Li, Z. Yin, T. Wang, et al., Gemcitabine and cisplatin regimen facilitates prognosis of advanced nasopharyngeal carcinoma, Cancer Med 7 (7) (2018) 2985–2992.