Observational Study

Medicine

OPEN

# Induction chemotherapy with sequential nimotuzumab plus concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma

## A retrospective real-world study

Danxian Jiang, MD[a], Jinxin Cao, MM[a], Linying Guo, MM[a], Yonghua Chen, BM[b], Ge Yuan[c], Jing Huang, MD[a,*]

**Abstract**

Many locally advanced nasopharyngeal carcinoma patients develop local recurrence or distant metastasis. Our retrospective real-world study aims to evaluate the efficacy and safety of curative sequential approach with induction chemotherapy followed by concurrent chemoradiation + nimotuzumab as first-line therapy in advanced nasopharyngeal carcinoma. From 2015 to 2021, the clinic data of 117 patients with advanced nasopharyngeal carcinoma (stage III–IV a) who were treated in the Affiliated Hospital of Guangdong Medical University were retrospectively reviewed. Fifty-four patients in observation group received taxanes, cisplatin, and 5-fluorouracil/taxanes and cisplatin induction chemotherapy and nimotuzumab (200 mg, weekly) combined with concurrent chemo-radiotherapy (cisplatin: 40 mg/m$^2$ weekly; intensity-modulated radiation therapy); 63 patients in control group received same therapy without nimotuzumab. There was no significant difference in patients' characteristic baseline between 2 groups ($P > .05$). The complete response rate and objective response rate of the observational group was significantly higher than control group (46.30% vs 17.64%, $P = .01$; 96.30% vs 82.54%, $P = .02$). The median follow-up time was 24.77 (3.53–65.97) months. Both of the median progress free survival time and overall survival time were not reached. The 5-year progression-free survival rate of observation group was greater than control group (84.40% vs 63.70%, hazard ratios 0.365, 95% confidence intervals 0.147–0.909, $P = .03$). The 5-year overall survival rate of observation group and control group were 91.70% and 84.60%, respectively ($P = .20$). None of the patients withdrew from the study due to adverse events. Nimotuzumab combined with concurrent chemoradiotherapy as first-line therapy in advanced nasopharyngeal carcinoma can improve objective response rate and 5-year progress free survival rate with good safety profile.

**Abbreviations:** CIs = confidence intervals, CR = complete response, DCR = disease control rate, EGFR = epidermal growth factor receptor, HRs = hazard ratios, IC = induction chemotherapy, IMRT = intensity-modulated radiation therapy, NCCN = the National Comprehensive Cancer Network, NPC = nasopharyngeal carcinoma, ORR = objective response rate, OS = overall survival, PD = disease progression, PF = cisplatin and 5-fluorouracil, PFS = progression-free survival, PR = partial response, TP = taxanes and cisplatin, TPF = taxanes, cisplatin and 5-fluorouracil.

**Keywords:** EGFR Mab, nasopharyngeal carcinoma, nimotuzumab, radiation and chemotherapy

## 1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor of the mucosal epithelium of the nasopharynx, which is one of the common malignant tumors in southern China. According to GLOBOCAN 2020, there were 1,33,354 new cases of nasopharyngeal cancer worldwide in 2020, including 80,008 deaths.[1–3] At present, the annual incidence of NPC in China is as high as 0.25% with the mortality of 0.14%.[4] The pathogenesis of NPC is still unclear, mainly related to infection, genetics, and environmental factors. Because nasopharyngeal cancer symptoms are not typical, the onset site is hidden; more than 70% of patients have been diagnosed as advanced stage initially.[5] The National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent chemoradiotherapy combined with adjuvant or induced chemotherapy combined with concurrent chemoradiotherapy as the preferred treatment for locally advanced NPC.

Under this situation, 20% to 30% of NPC patients will develop local recurrence or distant metastasis. So, the development of new specific drugs is of great significance.

Nimotuzumab is a highly humanized monoclonal antibody that can inhibit tumor angiogenesis, promote tumor

*The authors have no funding and conflicts of interest to disclose.*

*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

*[a] Department of Head and Neck Oncology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China, [b] Department of Pathology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China, [c] Department of Radiotherapy, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China.*

** Correspondence: Jing Huang, Department of Head and Neck Oncology, Affiliated Hospital of Guangdong Medical University, No. 57 South Renmin Avenue, Xiashan District, Zhanjiang 524001, China (e-mail: hj841023@163.com).*



*How to cite this article: Jiang D, Cao J, Guo L, Chen Y, Yuan G, Huang J. Induction chemotherapy with sequential nimotuzumab plus concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma: A retrospective real-world study. Medicine 2023;102:4(e32732).*

*Received: 18 November 2022 / Received in final form: 3 January 2023 / Accepted: 4 January 2023*

*http://dx.doi.org/10.1097/MD.0000000000032732*

cell apoptosis and antitumor cell proliferation. It has significant efficacy in various malignancies with less toxicity. As for NPC, the efficacy of nimotuzumab has been demonstrated already. A retrospective analysis from Liu et al[6] found that the 2-year overall survival (OS) in experimental group was 96.6%, which showed an obvious efficacy of nimotuzumab combined with concurrent chemoradiotherapy. The patients were generally well tolerated and there were no treatment-related deaths. Gao et al[7] found that the objective response rate (ORR) and disease control rate (DCR) of the experimental group and the control group were 78.5% versus 58.5% and 93.8% versus 80.0% ($P = .01$, $P = .02$), and the median OS of the 2 groups was (18.9 ± 3.6) and (16.3 ± 3.8) months, which were superior to those of the control group, adverse reactions are tolerable. But until now, the evidence of nimotuzumab on long-term (5-year progression-free survival [PFS] and OS) benefits is still insufficient. This study aimed to compare the treatment efficacy and safety of induction chemotherapy (IC) with sequential nimotuzumab plus concurrent chemoradiotherapy with chemoradiotherapy alone in patients with advanced NPC.

## 2. Methods

### 2.1. Patients

All consecutive cases of 117 patients with advanced NPC (AJCC 8th Edition) admitted to "The Affiliated Hospital of Guangdong Medical University" from 2015 to 2021 were included. Inclusion criteria: Aged 18 to 70; Karnofsky performance score ≥60 points; Histopathologic proof of undifferentiated non-keratinizing carcinoma of the nasopharynx; Clinical stage: III to IV a. Exclusion Criteria: Received other anti-tumor systemic therapy, including chemotherapy, targeted therapy, etc; Autoimmune diseases. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of Affiliated Hospital of Guangdong Medical University.

The tumor staging was based on AJCC 8th Edition staging system. Patient and tumor baseline characteristics (age, gender, Karnofsky performance score, TNM stage, clinic stage, and treatment in each group) were collected.

### 2.2. Treatment

***2.2.1. Control group.*** Patients had received taxanes, cisplatin and 5-fluorouracil (TPF)/taxanes and cisplatin (TP) IC with concurrent chemoradiotherapy.

***2.2.2. Observation group.*** Patients had received TPF/TP IC and sequential chemoradiotherapy, and also treatment of nimotuzumab.

Regimens included:

- TPF/TP IC (every 3 weeks for 3–4 cycles)

T: paclitaxel 135 to 175 mg/m$^2$ or docetaxel 75 mg/m$^2$ on day 1

P: cisplatin 75 mg/m$^2$ on day 1

F: 5-fu 500 mg/m$^2$ civ 120 hours or Tegafur, Gimeracil, and Oteracil Potassium capsules 40 to 60 mg/m$^2$ 1 to 14 days

- Concurrent chemoradiotherapy

Chemotherapy: cisplatin 40 mg/m$^2$ on days 1, every week for 7 to 9 weeks.

Radiotherapy: intensity modulated radiotherapy (IMRT) (RTOG 0615)

GTVnx: total dose 66 to 76 Gy for 32 to 33 fractions; GTVnd: total dose 66 to 70 Gy for 32 to 33 fractions; CTV1: total dose 60 to 62 Gy for 32 to 33 fractions CTV2: total dose 50 to 56 Gy for 32 to 33 fractions

Nimotuzumab: 200 mg intravenously every week for 7 to 9 weeks.

### 2.3. Efficacy and safety assessments

Imaging evaluation was performed 1 month after concurrent chemoradiotherapy, every 3 to 6 months within 2 years, and every 6 months within 2 to 5 years. If local tumor recurrence or distant metastasis was clinically suspected, imaging can be performed at any time.

Based on previous imaging data, the response was evaluated by response evaluation criteria in solid tumors referred to revised RECIST guideline (version 1.1).

Complete response (CR): Disappearance of all nasopharyngeal target lesions.

Partial response (PR): At least a 30% decrease in the sum of diameters of nasopharyngeal target lesions, taking as reference the baseline sum diameters.

Disease progression (PD): At least a 20% increase in the sum of diameters of nasopharyngeal target lesions and an absolute increase of at least 5 mm, or the appearance of new lesions.

Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Based on evaluable data, the ORR and DCR was calculated as follows.

PFS: Time from starting of induction therapy to tumor progression or death.

OS was determined based on the time from starting of induction therapy to death.

Based on the clinical recording in hospital, the adverse reactions were assessed according to CTCAE (version 5.0).

### 2.4. Statistical analysis

Statistical analyses used SPSS 22.0 (IBM Corp., Armonk, NY). For categorical variables, the percentages and frequencies were calculated. For the quantitative index, it is converted into the classification index to calculate the percentage and frequency. Analyses of patient characteristics at baseline, single factors, multivariate analysis and adverse reactions were conducted by the Chi-squared test for qualitative variables. Median overall survival (mOS) and progression-free survival (mPFS) were estimated from Kaplan–Meier curves. Differences in survival were assessed by using a 2-sided log-rank test The Cox proportional risk regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

## 3. Results

### 3.1. Patient characteristics

The patient characteristics of the 2 cohorts are summarized in Table 1. Of the 117 patients, 87 (74.36%) were male and 30 (25.64%) were female, aged 23 to 76 years, with 51 (43.59%) clinical stages III and 66 (56.41%) stage IV, and all patients were divided into 2 groups. In observation group, 35 (64.81%) of 54 patients received TPF and 19 (35.19%) received TP, as well as 49 (77.78%) of TPF, 14 (22.22%) of TP in control group. There was no significant difference in patient characteristics at baseline between 2 groups ($P > .05$).

### 3.2. Short-term efficacy

At the end of treatment, antitumor response of the 117 patients was analyzed. CR was observed in 25 (46.30%) of the 54 evaluable patients in observational group and in 11 (17.46%) of the 63 control patients. PR was observed in 27 patients of the observation group and in 41 patients of the control group. PD wasn't observed in observation group but in 7 patients of the control group, including 2 primary tumor progressions, 2 liver metastases,1 of cervical lymph node, lung and bone metastasis. stable disease was observed in 2 patients of the observation group and in 4 patients of the control group. The ORR

(96.30% vs 82.54%, $P = .02$) and DCR (100% vs 88.89%, $P = .02$) was higher in observational group, respectively (Table 2).

### 3.3. Long-term efficacy

The median follow-up time was 24.77 (3.53–65.97) months. The last follow-up date was 20 Oct, 2021. The 5-year PFS of observation group was greater than control group (84.40% vs 63.70%, HR 0.365, 95% CI 0.147–0.909, $P = .03$). The 5-year OS of observation group and control group were 91.70% and 84.60%, respectively ($P = .20$).

### 3.4. Analysis of survival risk factors

The Analyses of patient characteristics at baseline, single factors, and multivariate analysis were conducted by COX regression analysis (Figs. 1–3). The univariate analysis showed that age ($P = .05$) affected OS and group ($P = .03$), clinical stage ($P = .003$), M stage ($P < .001$), N ($P = .02$) stage and age ($P = .03$) affected PFS. The multivariate analysis showed that only clinical stage ($P = .01$) was statistical significance.

### 3.5. Adverse reactions

The adverse reactions mainly included gastrointestinal reactions, myelosuppression and mucosal damage. No patients had adverse reactions of grade 5 during the treatment and 1 month after treatment. In the stage of concurrent chemo-radiotherapy, no difference in adverse reactions occurred between the 2 groups (Table 3).

## 4. Discussion

Radiotherapy is the most important treatment for locally advanced NPC. Compared with conventional radiotherapy, IMRT can reduce the 5-year risk of local recurrence in newly diagnosed locally advanced NPC by 7.6%.[8] A meta-analysis

**Table 1**

**Patient characteristics.**

| Characteristics | Non-Nimotuzumab (N = 63) n (%) | Nimotuzumab (N = 54) n (%) | *P* value |
|---|---|---|---|
| Gender | | | .36 |
| Male | 49 (77.78%) | 38 (70.37%) | |
| Female | 14 (22.22%) | 16 (29.63%) | |
| Age | | | .81 |
| <55 yr | 43 (68.25%) | 38 (70.37%) | |
| ≥55 yr | 20 (31.75%) | 16 (29.63%) | |
| T stage | | | .11 |
| T1 | 1 (1.59%) | 1 (1.85%) | |
| T2 | 10 (15.87%) | 17 (31.48%) | |
| T3 | 34 (53.97%) | 19 (35.19%) | |
| T4 | 18 (28.57%) | 17 (31.48%) | |
| N stage | | | .33 |
| N0 | 1 (1.59%) | 4 (7.41%) | |
| N1 | 16 (25.40%) | 10 (18.52%) | |
| N2 | 27 (42.86%) | 27 (50.00%) | |
| N3 | 19 (30.16%) | 13 (24.07%) | |
| M stage | | | .28 |
| M0 | 57 (90.48%) | 52 (96.30%) | |
| M1 | 6 (9.52%) | 2 (3.70%) | |
| Clinical stage | | | .59 |
| III | 26 (41.27%) | 25 (46.30%) | |
| IV | 37 (58.73%) | 29 (53.70%) | |
| Kps | | | .74 |
| <90 | 7 (11.11%) | 5 (9.26%) | |
| ≥90 | 56 (88.89%) | 49 (90.74%) | |
| BMI | | | .71 |
| <18.5 | 19 (30.16%) | 18 (33.33%) | |
| ≥18.5 | 44 (69.84%) | 36 (66.67%) | |
| Induced chemotherapy | | | .12 |
| TPF | 49 (77.78%) | 35 (64.81%) | |
| TP | 14 (22.22%) | 19 (35.19%) | |
| Fluorouracil, n (%) | | | .64 |
| Tegafur, gimeracil, and oteracil potassium capsules | 27 (55.10%) | 18 (51.43%) | |
| 5-FU | 22 (44.90%) | 17 (48.57%) | |

BMI = body mass index, KPS = Karnofsky performance status, TP = taxanes and cisplatin, TPF = taxanes, cisplatin, and 5-fluorouracil.

**Table 2**

**Short-term efficacy.**

| | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|
| Non-nimotuzumab (n = 63) | 11 | 41 | 4 | 7 | 82.54% | 88.89% |
| Nimotuzumab (n = 54) | 25 | 27 | 2 | 0 | 96.30% | 100% |
| *P* | .001 | .10 | .69 | .02 | .02 | .02 |

CR = complete response, DCR = disease control rate, ORR = objective response rate, PD = disease progression, PR = partial response, SD = stable disease.

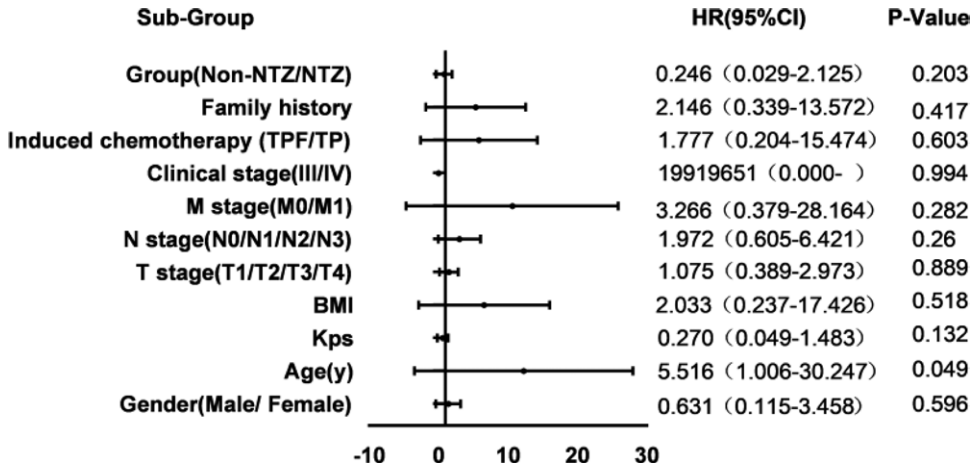


Figure 1. Univariate analysis of OS. OS = overall survival.

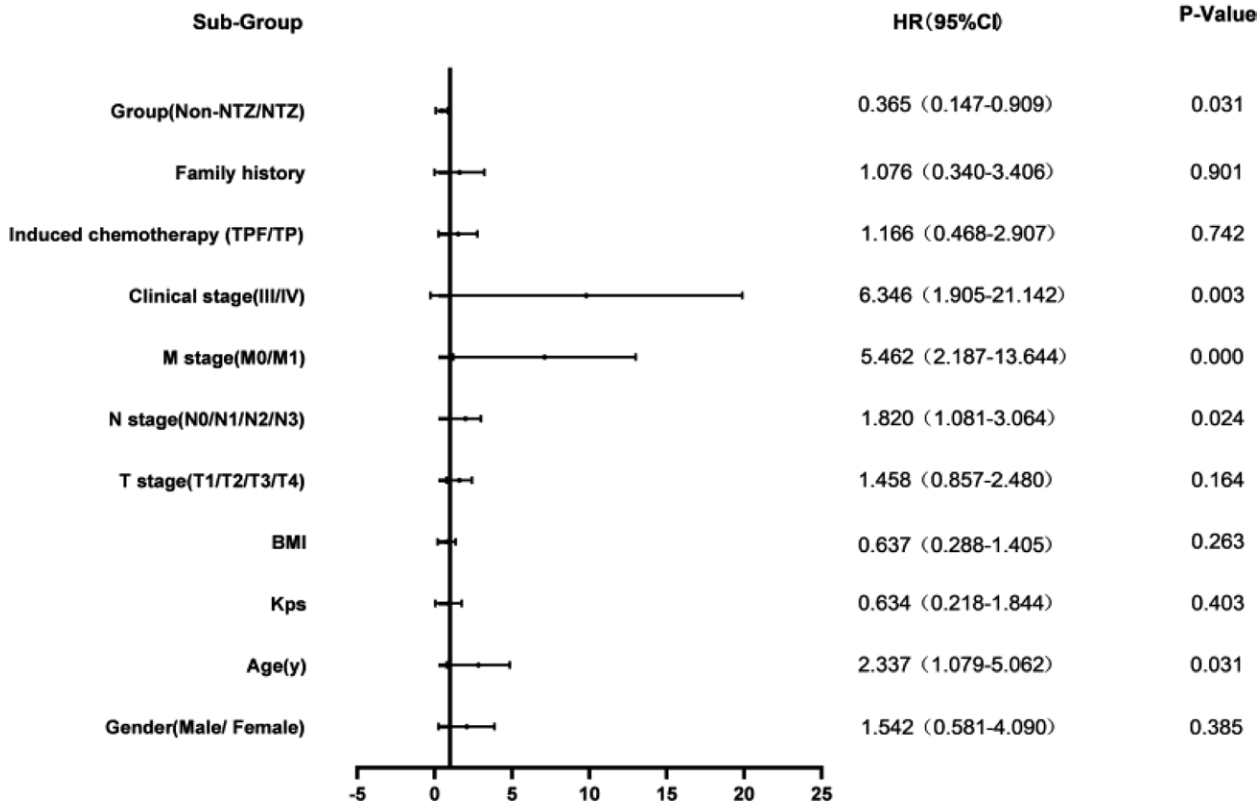


Figure 2. Univariate analysis of PFS. PFS = progression-free survival.

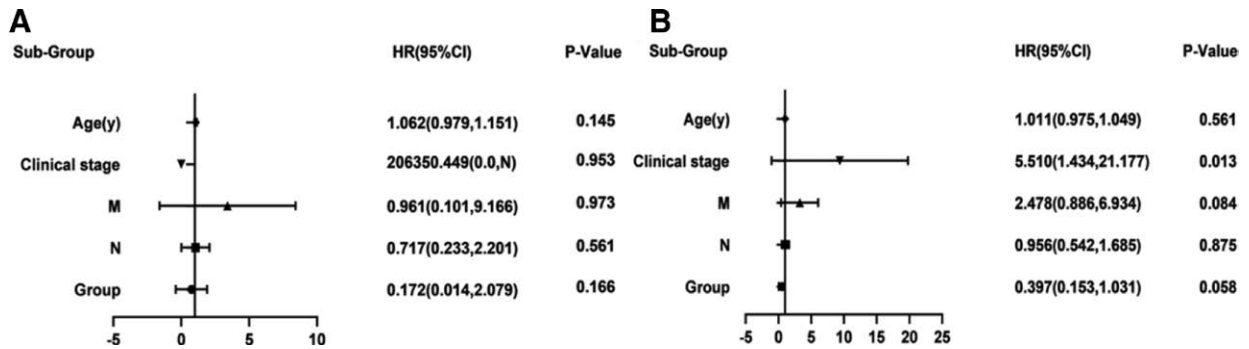


Figure 3. Multivariate analysis of OS and PFS. OS = overall survival, PFS = progression-free survival.

**Table 3**

**Adverse reactions.**

| | Non-Nimotuzumab (n = 63) | | | | Nimotuzumab (n = 54) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | I | II | III | IV | $x^2$ | *P* value |
| Mucous oral | 29 | 26 | 8 | 0 | 20 | 29 | 5 | 0 | 2.281 | .52 |
| Gastrointestinal | 31 | 30 | 1 | 1 | 26 | 26 | 1 | 1 | 0.502 | .97 |
| Myelosuppression | 6 | 25 | 4 | 2 | 20 | 19 | 3 | 3 | 3.996 | .41 |

including 3570 cases of NPC compared traditional 2D or 3D and IMRT. IMRT could significantly improve the 5-year local control rate and OS of NPC patients, and reduce complications such as delayed xerostomia, difficult oral closure, etc. caused by radiotherapy.[9] Although radiotherapy techniques are gradually improving, factors such as important nerves around the nasopharynx, tolerance, and high rate of serious adverse events limit the efficacy of radiotherapy. Factors such as side effects, chemo-radio resistance and organ tolerance of chemoradiotherapy limit the improvement of efficacy in patients with locally advanced NPC, so there is an urgent need for a new treatment with high response rate and low toxicity to be added to further improve the prognosis of NPC.[10] How to improve the OS and reduce the recurrence rate of patients with locally advanced NPC has become a hot topic in the medical field.

Ig-0099 study showed significant improvements in 3-year survival rate (78% vs 47%, $P = .001$) and 3-year PFS (69% vs 24%, $P < .001$) compared with radiotherapy alone.[11] NPC-9901 and NPC-9902 studies also confirmed the role of concurrent chemoradiotherapy in locally advanced NPC. The 5-year OS had a significant improvement of (72% vs 63%, $P = .04$).[12] As well as several other large clinical studies have reached similar conclusions, further confirming that chemoradiotherapy is superior to radiotherapy alone too.[13,14] Furthermore, NCCN guidelines recommend concurrent chemoradiotherapy combined with adjuvant as the preferred treatment for locally advanced NPC. Local recurrence and distant metastasis are the main causes of treatment failure.

IC is another therapy recommended by NCCN. It not only can reduce the volume of the primary tumor, but also reduce and kill the subclinical lesions, thus reducing the local recurrence and distant metastasis rate of the tumor.[15] The study of Chen et al[16] showed that the 5-year disease-free survival (DFS) (63.7% vs 29.5%, $P = .02$) and 5-year survival rate (74.5% vs 47.6%, $P = .01$) of patients induced by TP regimen were significantly improved compared with that of patients induced by TP regimen. Another Phase III trial in France confirmed cisplatin and 5-fluorouracil (PF) concurrent induced chemotherapy significantly increased 3-year PFS (HR 0.44, [95% CI 0.20–0.97]) and OS (HR 0.40, [95% CI 0.15–1.04]) benefits.[17] Another clinical study showed that PF induced chemotherapy combined with concurrent chemoradiotherapy increased the 3-year failure-free survival from 72% to 80% ($P = .03$), the 3-year distant failure-free survival increased from 83% to 90% ($P = .03$), and the 3-year OS increased from 86% to 92% ($P = .03$).[18] A comprehensive clinical study from high incidence areas of NPC demonstrated that IC concurrent chemoradiotherapy significantly improved OS (HR = 0.75, [95% CI, 0.57–0.99]), and improved the distant metastasis-survival by 4%.[19] Based on existing clinical studies, the 2018 NCCN guidelines changed the evidence for sequential concurrent chemoradiotherapy to class 2A for locally advanced NPC.

Epidermal growth factor receptor (EGFR) expresses more than 80% to 90% in NPC.[20] EGFR overexpression is one of the key factors leading to tumor cell proliferation, apoptosis inhibition, and tumor invasion and metastasis.[21,22] Therefore, anti-EGFR therapy has become a new treatment option. Nimotuzumab is a humanized monoclonal antibody against EGFR, as well as the humanization degree is up to 95%. The main anti-tumor mechanisms of nimotuzumab include: Binding to the extracellular region of EGFR, inhibiting tyrosine kinase activation; Involving the activation of the innate and adaptive immune response as an IgG1 antibody; Binding to tumor cells that overexpress the EGFR preferentially; Sparing normal cells with lower levels of the EGFR target; This mechanism of action ensures antitumor effects while has lower toxicity.[23] Also, nimotuzumab has been reported to increase radiosensitization.[24]

A phase III multi-center clinical study of TPF induced chemotherapy followed by radiotherapy combined with nimotuzumab or cisplatin in the treatment of locally advanced NPC showed that the 3-year OS comparison between cisplatin group and nimotuzumab group was 97% versus 89% ($P = .27$), 3-years PFS was 88% versus 79% ($P = .35$).[25] No significant difference in OS, PFS, distant metastasis free survival, and other aspects, but the safety of nimotuzumab was better. A multi-center clinical study was conducted on the induction of nimotuzumab combined with PF for locally advanced NPC. A total of 118 patients were enrolled and divided into 2 groups according to whether nimotuzumab was used in the TPF induce chemotherapy stage. The results showed that the cervical lymph node remission rate (CR + PR) was higher in the experimental group (81% vs 60%, $P = .04$), and nimotuzumab could reduce the occurrence of adverse reactions and improve the tolerance of patients to concurrent chemoradiation.[26]

Our study showed the CR rate of the observation group was 46.30% and that of the control group was 17.64%. The combination of nimotuzumab in the stage of concurrent chemoradiotherapy significantly improved the ORR (96.30% vs 82.54%, $P = .02$), DCR (100% vs 88.89%, $P = .02$). The 5-year PFS (84.40% vs 63.70%, HR 0.365, 95% CI (0.147–0.909), $P = .03$). These findings are consistent with the results of other similar studies.[27,28] The 5-year OS rate was 91.7% in observation group and 84.6% in the control group. It is not significant difference ($P = .20$), but it showed the trends. The median PFS and median OS were not reached in the 2 groups because the follow-up time was not long enough. The present study also analyzed the survival risk factors. Univariate analysis showed that age is the survival factors of OS, and the group, clinical stage, M stage, N stage and age are the survival risk factors of PFS. The multivariate analysis showed that only clinical stage was statistical significance of risk. For safety profile, nimotuzumab combined with concurrent chemoradiotherapy did not increase the incidence of grade 3 to 4 adverse reactions during concurrent chemo-radiotherapy. None of the patients had serious adverse reactions. This study supported that nimotuzumab was well tolerated in patients with concurrent chemoradiotherapy.

Herein, our study suggests that nimotuzumab combined with concurrent chemoradiotherapy could improve the ORR, DCR and 5-year PFS rate with lower toxicity. This regimen should be considered for patients with locally advanced combined factors (high tumor burden in cervical lymph nodes or other poor prognostic factors).

There were 3 limitations to the study. Due to the imperfect data of Epstein-Barr virus DNA in our hospital, the relevant data were not included in this study. This study was a retrospective study, the median PFS and median survival were not

reached in both groups because of the short follow-up time. Larger, long-term follow-up observations and prospective studies are needed to determine whether this regimen is beneficial for long-term survival.

## 5. Conclusion

Nimotuzumab combined with concurrent chemoradiotherapy for first-line treatment of advanced NPC can improve ORR and 5-year PFS rate with delightful safety benefits.

## Author contributions

**Data curation:** Danxian Jiang, Jing Huang.
**Formal analysis:** Danxian Jiang.
**Investigation:** Jinxin Cao, Ge Yuan.
**Methodology:** Yonghua Chen.
**Resources:** Yonghua Chen.
**Software:** Linying Guo.
**Writing – original draft:** Danxian Jiang, Jinxin Cao, Jing Huang.
**Writing – review & editing:** Jing Huang.

## References


[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
[2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
[3] Fu ZT, Guo XL, Zhang SW, et al. Incidence and mortality of nasopharyngeal carcinoma in China, 2014. Zhonghua Zhong Liu Za Zhi. 2018;40:566–71.
[4] Lv X, Cao X, Xia WX, et al. Induction chemotherapy with lobaplatin and fluorouracil versus cisplatin and fluorouracil followed by chemoradiotherapy in patients with stage III–IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomized, controlled, phase 3 trial. Lancet Oncol. 2021;22:716–26.
[5] Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys. 1992;23:261–70.
[6] Liu ZG, Zhao Y, Tang J, et al. Nimotuzumab combined with concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: a retrospective analysis. Oncotarget. 2016;717:24429–35.
[7] Gao M, Yuan T, Zhang F. Effect of nimotuzumab and PF induction chemotherapy combined with concurrent chemoradiotherapy in treating locally advanced nasopharyngeal carcinoma. J BUON. 2021;26:116–23.
[8] Mao YP, Tang LL, Chen L, et al. Prognostic factors and failure patterns in non-metastatic nasopharyngeal carcinoma after intensity-modulated radiotherapy. Chin J Cancer. 2016;35:103.
[9] Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. Oral Oncol. 2015;51:1041–6.
[10] Guan S, Wei J, Huang L, et al. Chemotherapy and chemo-resistance in nasopharyngeal carcinoma. Eur J Med Chem. 2020;207:112758.
[11] Al-Sarraf M, LeBlanc M, Giri P, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol. 1998;16:1310–7.
[12] Lee AW, Tung SY, Ngan RK, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. Eur J Cancer. 2011;47:656–66.
[13] Lin JC, Jan JS, Hsu CY, et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol. 2003;21:631–7.
[14] Chen Y, Sun Y, Liang SB, 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. 2013;119:2230–8.
[15] Ribassin-Majed L, Marguet S, Lee AWM, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma?. An individual patient data network meta-analysis. J Clin Oncol. 2017;35:498–505.
[16] Chen W, Zhong WM, Yu H, et al. Efficacy of induction chemotherapy combined with concurrent chemoradiotherapy for advanced nasopharyngeal carcinoma. Guangxi Med J. 2017;39:263–5.
[17] Frikha M, Alperin A, Tao Y, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). Ann Oncol. 2018;29:731–6.
[18] Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomized controlled trial. Lancet Oncol. 2016;17:1509–20.
[19] Chen YP, Tang LL, Yang Q, et al. Induction chemotherapy plus concurrent chemoradiotherapy in endemic nasopharyngeal carcinoma: individual patient data pooled analysis of four randomized trials. Clin Cancer Res. 2018;24:1824–33.
[20] Lang J, Gao L, Guo Y, et al. Comprehensive treatment of squamous cell cancer of head and neck: Chinese expert consensus 2013. Future Oncol. 2014;10:1635–48.
[21] Sevelda F, Mayr L, Kubista B, et al. EGFR is not a major driver for osteosarcoma cell growth in vitro but contributes to starvation and chemotherapy resistance. J Exp Clin Cancer Res. 2015;34:134.
[22] Hatanpaa KJ, Burma S, Zhao D, et al. Epidermal growth factor receptor in glioma: signal transduction, neuropathology, imaging, and radioresistance. Neoplasia. 2010;12:675–84.
[23] Wu F, Wen Z, Wu X, et al. Obserbation on the efficacy of nimotuzumab combined with concurrent chemoradiotherapy in the treatment of nasopharyngeal carcinoma. Clin Med Engineer. 2019;26:1701–2.
[24] Chua DT, Wei WI, Wong MP, et al. Phase II study of gefitinib for the treatment of recurrent and metastatic nasopharyngeal carcinoma. Head Neck. 2008;30:863–7.
[25] Liao XY, Kong L, Zheng H, et al. Comparison of efficacy and adverse reactions between radiotherapy combined with cisplatin and radiotherapy combined with nimotuzumab in treatment of locally advanced nasopharyngeal carcinoma. Chin J Radiat Oncol. 2016;25:1277–80.
[26] Lu Y, Chen D, Liang J, et al. Administration of nimotuzumab combined with cisplatin plus 5-fluorouracil as induction therapy improves treatment response and tolerance in patients with locally advanced nasopharyngeal carcinoma receiving concurrent radiochemotherapy: a multicenter randomized controlled study. BMC Cancer. 2019;19:1262.
[27] Zhang S, Huang X, Zhou L, et al. An open-label, single-arm phase II clinical study of induction chemotherapy and sequential nimotuzumab combined with concurrent chemoradiotherapy in N3M0 stage nasopharyngeal carcinoma. J BUON. 2018;23:1656–61.
[28] Patil VM, Noronha V, Joshi A, et al. A randomized phase 3 trial comparing nimotuzumab plus cisplatin chemoradiotherapy versus cisplatin chemoradiotherapy alone in locally advanced head and neck cancer. Cancer. 2019;125:3184–97.