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Efficacy of concurrent chemoradiotherapy combined with nimotuzumab for low-risk T4 stage nasopharyngeal carcinoma

A pilot study

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Abstract

Background: The purpose of this study was to analyze the efficacy and safety of concurrent chemoradiotherapy combined with Nimotuzumab for low-risk T4 stage nasopharyngeal carcinoma (NPC).

Methods: This study included 49 low-risk T4 stage NPC patients treated with concurrent chemoradiotherapy plus Nimotuzumab. The IMRT doses were planning target volume (PTV) 70–72 Gy for gross disease in the nasopharynx, and 66–70 Gy for positive lymph nodes. The doses for high risk and low risk region PTV were 60–62 Gy and 54–56 Gy in 31-33 fractions. All patients received a chemotherapy program consisting of Cisplatin 100mg/m2, day 1, Q3w and were treated by Nimotuzumab (Nimotuzumab 200mg, iv, Qw).

Results: All 49 patients completed at least two cycles of chemotherapy and seven weeks of Nimotuzumab. The total efficiency of therapy was 100.0%. The 3-year overall survival (OS), distant metastasis-free survival (DMFS), local-regional control (LRC) and progression-free survival (PFS) rates were 89.7%, 87.8%, 97.9% and 85.7%, respectively. No regional lymph node recurrence was detected. The most serious acute toxicity was mucositis, with prevalence of Grades 0 to IV being 0.0%, 57.1%, 34.7%, 8.2%, and 0.0%, respectively. Late toxicity manifested as Grades I and II xerostomia in 32 and 10 patients.

Conclusion: In patients with low-risk T4 stage NPC, concurrent chemoradiotherapy combined with Nimotuzumab yielded an excellent local control rate, and the toxicities were mild and tolerable. Distant metastasis was the main cause of treatment failure.

Abbreviations: AJCC = American Joint Committee on Cancer, CR = complete response, CT = computed tomography, CTV = clinical target volume, DMFS = distant metastasis-free survival, EBV = Epstein–Barr virus, ECT = electroconvulsive therapy, EGFR = epidermal growth factor receptor, GTV = gross tumor volume, ICRU = International Commission on Radiation Units and Measurements, IMRT = intensity-modulated radiotherapy, LRC = local-regional control, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NPC = nasopharyngeal carcinoma, OS = overall survival, PET = positron emission tomography, PFS = progression-free survival, PR = partial response, PTV = planning target volume, RECIST = Response Evaluation Criteria In Solid Tumors, RTOG = Radiation Therapy Oncology Group, SIB = simultaneous-integrated boost, VEGFR = vascular endothelial growth factor receptor.

Keywords: chemotherapy, intensity-modulated radiotherapy (IMRT), nasopharyngeal carcinoma (NPC), nimotuzumab, prognosis

1. Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in southeastern China. Intensity-modulated radiation therapy (IMRT) is superior to conventional techniques in radiotherapy, with respect to technical advantages, local or regional control, minimizing damage to critical organs, and treatment outcomes. IMRT produces superior dose distributions with improved tumor coverage and lower doses to normal tissues. Clinical studies have shown that NPC patients treated with IMRT with at least 66.5 Gy during IMRT have significantly less locoregional failure.[1]

Although early-stage NPC is highly curable using IMRT alone, approximately 70% of newly diagnosed NPC patients present with advanced diseases (stage III or IV) and are prone to locoregional recurrence or distant metastases after IMRT. The local residual rate of NPC is about 10% and local recurrent rate ranges from 16.8% to 23%, depending on the initial tumor status.[2,3] There is a certain regularity in local recurrent, about 50% occurred within 2 years, 80% to 90% in 5 years, rarely occur after 5 years. Studies have shown that recurrence mainly in the field of radiation, accounting for 50% to 72%, marginal recurrence, and field recurrence is quite less.[4]

Local control rate of T4 stage is the lowest in NPC, with 70% to 80% in 5 years. Low-risk means to N0 and N1 stages, because the risk of distant metastasis is relatively low in this part of the patient. Altered epidermal growth factor receptor (EGFR) signaling is widely implicated in cell apoptosis resistance,

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proliferation, radiotherapy resistance, metastasis, and invasion. Overexpression of EGFR is a feature of NPC, and 95% to 100% of high EGFR expression was associated with a targeted drug therapy. Nimotuzumab is a humanized anti-EGFR monoclonal antibody that is obtained by replacing a murine complementary-determining region with a human framework and designed to reduce immunoreactivity and to enhance radio sensitivity. Irradiation combined with Nimotuzumab has shown clinical efficacy in improving locoregional control and OS in NPC and was loaded in "NCCN Clinical Practice Guidelines (Chinese version) in March 2009.[5] The aim of the study was to investigate whether low-risk T4 stage NPC treatment could be optimized by concurrent chemoradiotherapy combined with Nimotuzumab.

2. Materials and methods

2.1. Ethical statement

This study was reviewed and approved by the Ethics Committee of Hainan General Hospital, Haikou, China. Informed consent was obtained from each patient.

2.2. Patients

We analyzed data from 49 patients with low-risk T4 stage NPC who were treated in our clinic between July 2013 and June 2014. These patients had histologically confirmed non-keratinizing carcinoma without distant metastasis. Clinical and laboratory examinations included plasma Epstein–Barr virus (EBV) DNA load, magnetic resonance imaging (MRI) of the head and neck region, chest and abdominal computed tomography (CT), and electroconvulsive therapy (ECT) for exclusion of distant metastases. The NPC patients were classified according to the 7th Edition of American Joint Committee on Cancer (AJCC) TNM classification. The clinical characteristics of the patients included in the study are summarized in Table 1.

Table 1

Clinical characteristics of NPC patients.

Characteristic	Patients (n)	% of patients
Age, y		
Median	51	
Range	19–70	
Sex		
Male	34	69.4
Female	15	30.6
Nonkeratinizing		
Undifferentiated type	33	67.3
Differentiated type	16	32.7
N stage		
0	9	18.4
1	40	81.6
Response rate		
CR	38	77.6
PR	11	22.4
NC	0	0
PD	0	0
EB DNA		
≥5.0E+2 copies/mL	35	71.4
<5.0E+2 copies/mL	14	28.6

2.3. IMRT

IMRT was delivered by using a simultaneous-integrated boost (SIB) technique. The nasopharynx gross tumor volume (GTVnx) and positive neck lymph nodes (GTVnd) were evaluated by MRI. We defined and sketched the target area according to International Commission on Radiation Units and Measurements (ICRU) No. 83 Report. The planning target volume (PTV) was created, based on each GTV and clinical target volume (CTV) with an additional 3 mm margin. PTV approaching the brain and spinal cord were shrunk accordingly. The prescribed doses were PTV 70 to 72 Gy for gross disease in nasopharynx, and 66 to 70 Gy for positive lymph nodes in 31 to 33 fractions. The prescribed doses for high-risk and low-risk region PTV were 60 to 62 and 54 to 56 Gy in 31 to 33 fractions, respectively.

2.4. Chemotherapy and targeted drug therapy

All patients received a concurrent chemotherapy program consisting of cisplatin 100 mg/m^2, day 1, Q3w, and were treated by nimotuzumab (200 mg, iv, Qw). The time of each infusion for nimotuzumab is not less than 1.5 hours. The preventive anti-allergy treatment was needed completely.

2.5. Follow-up

Patients were scheduled for follow-up visits every 3 months for the first 2 years, every 6 months for the 3 following years, and annually thereafter. Each follow-up included chest X-ray, abdominal ultrasound, and endoscopy. MRI of the head and neck and ECT were performed every 6 months. Positron emission tomography (PET) was optional in high-risk cases. Toxicities were observed and scored according to the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG). Efficacy was determined using the RECIST solid tumor efficacy evaluation criteria.

2.6. Statistical analysis

Data were processed using SPSS 21.0 software (SPSS Inc., Chicago, Illinois). The Kaplan–Meier test was used to calculate overall survival (OS), distant metastasis-free survival (DMFS), local-regional control (LRC), and progression-free survival (PFS) rates. Comparison between groups for the frequency of data was carried out using the Chi-square test, and independent risk factors were analyzed using the Cox proportional hazards model. P values $<.05$ were considered statistically significant.

3. Results

3.1. Response rates

Three months after IMRT, the total efficiency of therapy was 100.0% including the nasopharynx lesion and neck region. There were 38 (77.6%) and 11 (22.4%) cases of CR and PR, respectively. The CR rates in the groups with retropharyngeal lymph nodes greater than 1 cm were inferior to those of less than 1 cm ($P = .006$). The same result was not observed in the groups with the maximum diameter of nasopharyngeal tumor larger than 3.5 cm and smaller than 3.5 cm ($P > .05$).

3.2. Patterns of failure

Patients were monitored for 15 to 50 months, with a median follow-up duration of 42 months. There were 5 deaths, including recurrent NPC (1 case) and distant metastasis (4 cases). The overall failure rate was 12.2% (7 patients), including 1 local recurrence. This relapse occurred inside the nasopharyngeal

cavity in 16 months after the end of radiotherapy. Distant metastasis was the main cause of failure. There were 6 patients with distant metastases (12.2%); the common metastasis site was bone (2 cases), lung (1 cases), liver (1 cases), and multiple locations (2 cases). The median distant metastasis time was 17 months (range, 6–32 months).

3.3. Survival analysis

The 3-year OS, DMFS, LRC, and PFS rates were 89.7%, 87.8%, 97.9%, and 85.7%, respectively (Figs. 1–4). No regional lymph node recurrence was detected. Further analyses revealed that gender, age, tumor diameter, EBV-DNA > 4.0E+3 copies/mL, regularity of radiotherapy (interruption ≥5 days), and severe chemoradiotherapy complications (≥ grade III) were not significantly associated with the prognosis of patients (all $P > .05$) (Table 2).

3.4. Toxicities

All 49 patients completed at least 2 cycles of chemotherapy and 7 weeks of Nimotuzumab. The acute toxicities included mucositis, xerostomia, dermatitis, and myelosuppression (Table 3). The total incidence of severe (≥ grade III) acute toxicities was 12.2% (6 cases). The chronic toxicities mainly were grade I (32 cases) and grade II (10 cases) radioactive xerostomia, which intensified 3 to 6 months after radiotherapy. In addition, there was 1 case (2.0%) of radiation encephalopathy, 3 cases (6.1%) of posterior nasal concha, 18 cases (36.7%) of hearing loss, and 15 cases (30.6%) of neck skin fibrosis.

4. Discussion

According to statistics released by China Cancer Center in 2015, more than 60,000 cases of NPC were newly diagnosed each year, with more than 34,000 deaths. However, the incidence of NPC in other countries of the world continued to decline more than 20% in the past 30 years.[6,7] Concurrent chemoradiotherapy along with adjuvant chemotherapy has become the standard treatment for local advanced NPC, as stated in the NCCN Guidelines. But adjuvant chemotherapy has failed to be an independent prognostic factor in multivariate analysis for treatment combined with IMRT during these years. These studies have demonstrated that concurrent and adjuvant chemotherapy do not provide significant additive effects on the survival rates in advanced NPC patients treated with IMRT. Instead, the therapies would increase acute and late complications.[8–10]

The main reasons for recurrence can be divided into biological factors and clinical factors. Biological factors meant that tumor clonogenic cells showed resistance to radiation, which commonly cannot be completely killed by routine radiation dose. There were still small residual lesions after radical radiotherapy; these lesions would proliferate to form recurrence lesions. Clinical factors referred to a relapse of the lack of radiation dose in the tumor tissue; the common cause was that the scope of tumor invasion and positive lymph node evaluation were not accurate. Many factors led to inadequate irradiation for partial tumors, including cold spots in target area, body position, positioning error, and so on.

Targeted drug therapy is a new therapeutic approach for NPC, mainly including 2 intervention targets such as EGFR and vascular endothelial growth factor receptor (VEGFR) .

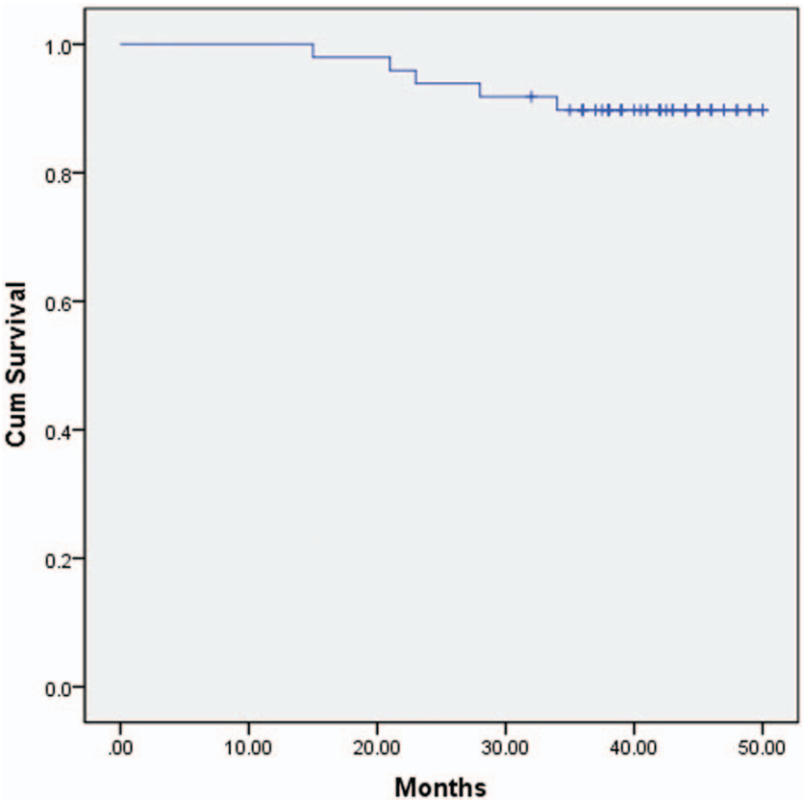

Figure 1. Kaplan–Meier estimate of overall survival (OS) for nasopharyngeal carcinoma patients treated with concurrent chemoradiotherapy and Nimotuzumab.

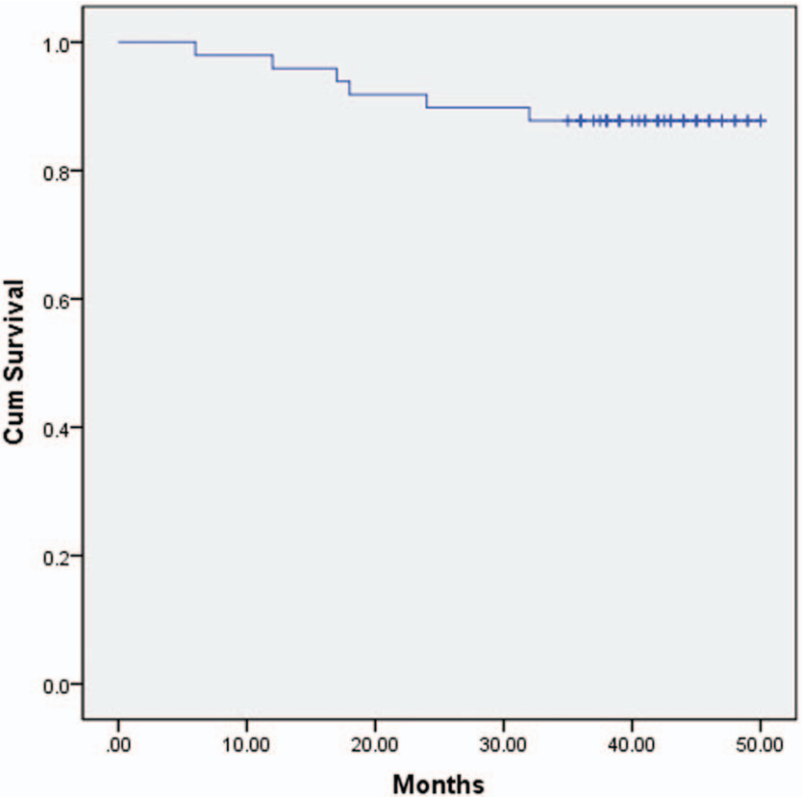

Figure 2. Kaplan–Meier estimate of distant metastasis-free survival (DMFS) for nasopharyngeal carcinoma patients treated with concurrent chemoradiotherapy and Nimotuzumab.

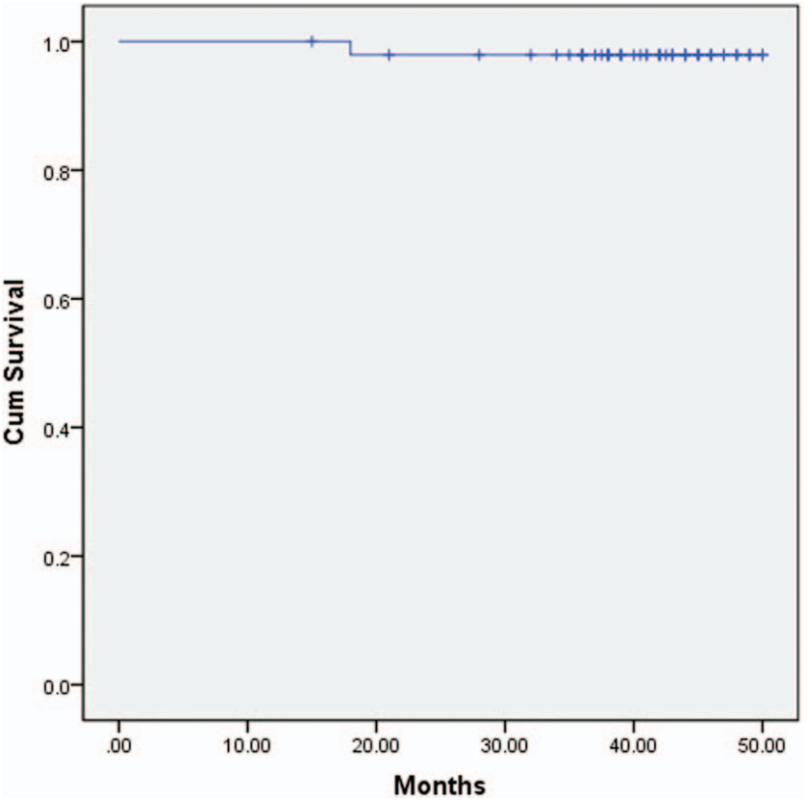

Figure 3. Kaplan–Meier estimate of local-regional control (LRC) for nasopharyngeal carcinoma patients treated with concurrent chemoradiotherapy and Nimotuzumab.

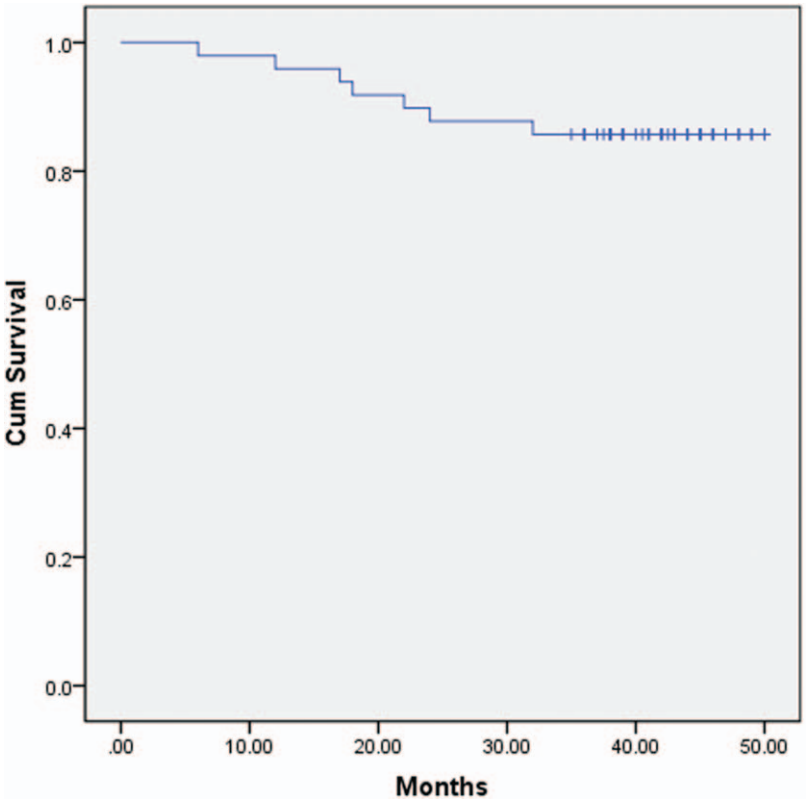

Figure 4. Kaplan–Meier estimate of progression-free survival (PFS) for nasopharyngeal carcinoma patients treated with concurrent chemoradiotherapy and Nimotuzumab.

Nimotuzumab is the first monoclonal antibody targeting EGFR in the world, and the total effective rate was more than 90% in local advanced NPC by chemoradiotherapy and nimotuzumab. After intravenous injections of 50, 100, 200, and 400 mg, the elimination half-life of Nimotuzumab were 62.92, 82.60, 302.95, and 304.52 hours.[11,12] In order to ensure the plasma concentration of nimotuzumab once a week, we chose to synchronized 200 mg nimotuzumab combined with chemoradiotherapy.

In the present study, the short-term effect of the group was 100.0%, in which 38 cases (77.6%) reached CR. The efficiencies observed in our study were very satisfactory compared with the previous reports in our clinic[6] and also better than those of IMRT with chemotherapy, with local control and regional control being more prominent.[10,13] Because the short-term efficiencies and local control rates were between 90% and 95% in local advanced NPC as reported in our hospital and the above literatures, this study was enrolled in patients with T4 stage. These tumor volumes were larger, and the radiation-resistant cells were more, but the adverse reactions were alleviated. So, the results were more exciting and satisfying. No regional lymph node recurrence was detected, and the CR rates in the groups with retropharyngeal lymph nodes greater than 1 cm were inferior to those of less than 1 cm. The 3-year OS, DMFS, LRC, and PFS rates were 89.7%, 87.8%, 97.9%, and 85.7%, respectively. Pathological analysis again found that tumor tissue contained a sarcoma component in the only 1 recurrence. If this type of tumor was not sensitive to radiotherapy, simply increasing the dose or changing the fractionation schedule might not improve the local control rate; other therapy such as immunotherapy or radiosensitizing agents should be recommended. Skull bone relapse must be identified with skull base necrosis, as far as possible to obtain pathology. If you cannot get

Table 2

Impact of prognostic factors on OS by multivariate analysis.

	Multivariate analysis	
Variable	***P***	**HR (95% CI)**
Gender	.217	3.852 (0.422–38.064)
Age	.503	0.625 (0.192–2.936)
Tumor diameter	.559	0.937 (0.107–5.842)
EBV-DNA	.189	0.242 (0.027–2.515)
Regularity of RT	.105	9.041 (0.763–77.105)
Complications	.376	2.939 (0.495–9.281)

CI = confidence interval, HR = hazard ratio.

Table 3

Acute toxicities during IMRT.

	Grade				
Acute toxicities	**0 (%)**	**I (%)**	**II (%)**	**III (%)**	**IV (%)**
Dermatitis	5 (10.2)	41 (83.7)	3 (6.1)	0 (0)	0 (0)
Mucositis	0 (0)	28 (57.1)	17 (34.7)	4 (8.2)	0 (0)
Xerostomia	0 (0)	35 (71.4)	14 (28.6)	0 (0)	0 (0)
Vomiting	3 (6.1)	36 (73.5)	10 (20.4)	0 (0)	0 (0)
Hair loss	29 (59.2)	18 (36.7)	2 (4.1)	0 (0)	0 (0)
WBC	27 (55.1)	17 (34.7)	4 (8.2)	1 (2.0)	0 (0)
NEU	33 (67.3)	12 (24.5)	3 (6.1)	1 (2.0)	0 (0)
HGB	17 (34.7)	32 (65.3)	0 (0)	0 (0)	0 (0)

the pathology, PET before and after hyperbaric oxygen treatment can help to distinguish changes. Further analyses revealed that gender, age, tumor diameter, EBV-DNA > 4.0E+3 copies/mL, regularity of radiotherapy (interruption ≥5 days), and severe chemoradiotherapy complication (≥ grade III) were not significantly associated with the prognosis of patients. The total incidence of severe (≥ grade III) acute toxicities was 12.2% (6 cases), the incidence and extent of mucositis are tolerable, and late adverse reactions are also acceptable. Our results on treatment failure indicate that distant metastasis was the major factor affecting treatment outcome.

In summary, concurrent chemoradiotherapy combined with Nimotuzumab in low-risk T4 stage NPC was feasible and resulted in a better local control rate. The side effects of treatment were generally tolerated. Future studies should synchronize chemoradiotherapy with more targeted drug therapy in large-scale prospective clinical studies.

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Writing – original draft: shuai zhang.
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