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ARTICLE

Nimotuzumab Combined with Neoadjuvant or Induction Chemotherapy for Head and Neck Squamous Cell Carcinoma: A Retrospective Study

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ABSTRACT

Objective: To assess the efficacy and toxicity of nimotuzumab combined with neoadjuvant or induction chemotherapy for head and neck squamous cell carcinoma (HNSCC). **Methods:** Patients received intravenous nimotuzumab (400 mg, weekly for 1–3 weeks) combined with chemotherapy (5-fluorouracil/paclitaxel/docetaxel + nedaplatin/cisplatin for 1–2 cycles), prior to definitive surgical resection, radiotherapy or other treatments. The primary endpoint was the objective response rate (ORR). The secondary endpoints were tumor downstaging, complete response rate (CRR), partial response rate (PRR), disease control rate (DCR), R0 resection rate, pathological complete response (pCR), larynx preservation rate, overall survival (OS), progression-free survival (PFS), and safety. **Results:** A total of 71 HNSCC patients with $T_{1\text{-}4}N_{0\text{-}2}M_0$ were enrolled. After neoadjuvant/induction chemotherapy, the ORR in patients with hypopharyngeal and laryngeal cancer was 100% and 76.1%, respectively. The DCR was 100% in both groups. The T downstaging in patients with hypopharyngeal and laryngeal cancer was 64.0% and 50.0%, the N downstaging was 28.0% and 2.2% ($p = 0.001$), respectively. At the early stage and locally advanced stage, the T downstaging was 66.7% and 50.0%, the N downstaging was 0% and 16.0% ($p = 0.128$), respectively. The R0 resection rate and pCR in 39 patients receiving surgery were 94.9% and 20.5%, respectively. The larynx preservation rate was 73.2%. The median PFS was 29.2 months in patients with laryngeal cancer. A mild rash occurred in a single patient and no grade 4 adverse events were encountered. **Conclusion:** Nimotuzumab combined with neoadjuvant or induction chemotherapy achieved similar short-term efficacy and less adverse events compared with previous studies. The N downstaging rate in patients with hypopharyngeal cancer was significantly higher compared with patients with laryngeal cancer.

KEYWORDS

Down-staging; head and neck squamous cell carcinoma; nimotuzumab

1 Introduction

About 745,000 new cases and 365,000 new deaths from head and neck carcinomas were described worldwide in 2020. Among them, 269,000 new deaths were reported from hypopharyngeal cancers and 138,000 deaths were reported from laryngeal cancer [1]. Head and neck carcinomas rank sixth in frequency, with more than 60% of patients presenting at stage III or IV [2]. Hypopharyngeal and laryngeal cancer patients are often diagnosed at an advanced stage, while patients at earlier stages benefit

from surgery or radiotherapy alone. Locally advanced patients require total laryngectomy followed by radiotherapy or chemoradiotherapy [3–6], especially for squamous cell cancer [7,8]. Chemotherapy or induction chemotherapy before surgery is an alternative to a total laryngectomy, achieving better larynx preservation rates without affecting the patients' survival [9,10]. Induction chemotherapy can significantly improve the patient's survival and laryngeal preservation, with the TPF regimen (docetaxel, carboplatin, and fluorouracil) increasing the rate of laryngeal preservation by more than 70% [11–14].

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein of the Erb-B family that regulates various cellular functions, including apoptosis, angiogenesis, cell proliferation, migration, and invasion. EGFR overexpression is widely observed in various cancer cells, including head and neck cancer, breast cancer, and cervical cancer [15–18]. Nimotuzumab is a humanized monoclonal antibody against EGFR, inhibiting the proliferation of tumor cells and promoting apoptosis. Nimotuzumab has been marketed in more than 20 countries for the treatment of advanced head and neck squamous cell cancer (HNSCC), nasopharyngeal carcinoma, glioma, and locally advanced esophageal cancer. Treatment combinations with nimotuzumab are safe and provide a therapeutic option for locally advanced nasopharyngeal carcinoma and HNSCC [19–24].

A few studies investigated nimotuzumab plus induction chemotherapy or concurrent chemoradiotherapy in patients with hypopharyngeal and laryngeal cancer. This study assessed the efficacy and toxicity of nimotuzumab combined with neoadjuvant or induction chemotherapy for HNSCC, especially in patients with hypopharyngeal and laryngeal cancer.

2 Patients and Methods

2.1 Patients

We retrospectively analyzed patients treated with nimotuzumab plus neoadjuvant or induction chemotherapy at the Second Affiliated Hospital of Xi'an Jiaotong University (China) from November 29, 2018 to April 13, 2021. The lesions were histologically confirmed as hypopharyngeal and laryngeal cancer. We collected different types of data, including demographic information, primary tumor location, clinical staging, and the Karnofsky performance status (KPS) score. Efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and while adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (reference: 2021229) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to enrollment.

2.2 Methods

HNSCC patients received intravenous nimotuzumab (400 mg, weekly for 1–3 weeks; Biotech Pharmaceuticals Co., Ltd., Beijing, China) combined with chemotherapy (5-fluorouracil/paclitaxel/docetaxel + nedaplatin/cisplatin for 1–2 cycles) (5-fluorouracil: Shanghai Xudong Haipu Pharmaceutical Co., Ltd., Shanghai, China; Paclitaxel: Nanjing Sike Medicine Industry Co., Ltd., Nanjing, China; Docetaxel: Jiangsu Aosaikang Pharmaceutical Co., Ltd., Nanjing, China; Nedaplatin: Jiangsu Aosaikang Pharmaceutical Co., Ltd., Nanjing, China; Cisplatin: QILU Pharmaceutical Co., Ltd., Jinan, China) prior to definitive surgical resection, radiotherapy or other treatments. The primary endpoint was the tumor objective response rate (ORR). The secondary endpoints consisted of tumor down-staging, complete response rate (CRR), partial response rate (PRR), disease control rate (DCR), R0 resection rate, pathological complete response (pCR), larynx preservation rate, overall survival (OS), progression-free survival (PFS), and safety.

2.3 Statistical Analysis

Data were analyzed with SPSS 21.0 (IBM, Chicago, Illinois, USA). Continuous variables are described as mean ± standard deviation (SD). Categorical variables are described using either percentages or

frequencies. Quantitative variables were compared by using the *t*-test while qualtitative variables were compared by using the chi-squared test. Survival curves were plotted using the Kaplan-Meier method with a two-sided log-rank test (significance level of 5%). A p value < 0.05 was considered statistically significant.

3 Results

3.1 Patients' Characteristics

A total of 71 HNSCC patients with $T_{1\text{-}4}N_{0\text{-}2}M_0$ were enrolled. There were 25 patients (35.2%) diagnosed with hypopharyngeal carcinoma and 46 patients (64.8%) diagnosed with laryngeal carcinoma. Twenty-one patients (29.6%) were diagnosed at an early stage ($T_1N_{any}M_0 + T_2N_0M_0$) and 50 patients (70.4%) were diagnosed at a locally advanced stage, according to the American Joint Committee on Cancer (AJCC, 8th edition). Data including age, sex, weight, KPS, concomitant diseases, smoking, and alcohol habits were collected at the baseline (Table 1).

Table 1: Baseline of characteristics

Category	n (%)
Age (mean ± SD, years)	62.3 ± 9.0
Sex	
Male	67 (94.4%)
Female	4 (5.6%)
Body weight (mean ± SD, Kg)	68.6 ± 9.7
KPS score (mean ± SD)	87.3 ± 7.0
If has concomitant diseases	
Yes	32 (40.1%)
No	39 (54.9%)
Smoking history	
≥40 years	17 (23.9%)
≤30–40 years	26 (36.6%)
≤20–30 years	7 (9.9%)
≤10–20 years	3 (4.2%)
≤10 years	1 (1.4%)
No	17 (23.9%)
Alcohol habits	
Yes	26 (36.6%)
No	45 (63.3%)
Primary tumor location	
Hypopharynx	25 (35.2%)
Larynx	46 (64.8%)
T stage	
T1	2 (2.8%)

(Continued)

Table 1 (continued)	
Category	n (%)
T2	22 (31.0%)
T3	42 (59.2%)
T4	5 (7.0%)
N stage	
N0	53 (74.6%)
N1	12 (16.9%)
N2	6 (8.5%)
Clinical stage[a]	
Early stage (I + II)	21 (29.6%)
Local-advanced stage (III + IV)	50 (70.4%)

Note: [a]AJCC 8th edition.

3.2 Short-Term Efficacy

The ORR in patients at the early stage (I + II) and locally advanced stage (III + IV) was 95.2% (20/21) and 80.0% (40/50), respectively. When patients were grouped by primary tumor location, the ORR was 100% (25/25) and 76.1% (35/46) in the hypopharyngeal group and laryngeal group, respectively. The CRR, PRR, and DCR in patients at the early stage were 28.6% (6/21), 66.7% (14/21), and 100% (21/21), respectively. The CRR, PRR, and DCR in patients at the locally advanced stage were 12.0% (6/50), 68.0% (34/50), and 100% (50/50) (all $p > 0.05$) The CRR, PRR, and DCR in the hypopharyngeal group were 20% (5/25), 80.0% (20/25), and 100% (25/25), respectively. The CRR, PRR, and DCR in the laryngeal group were 15.2% (7/46), 60.9% (28/64), and 100% (25/25), respectively (all $p > 0.05$) (Table 2).

Table 2: Short-term efficacy

Category[a]	CRR	PRR	ORR	DCR	R0 resection	pCR	Larynx preservation rate
	n (%)						
Clinical stage							
Early stage (I + II) (n = 21)	6 (28.6%)	14 (66.7%)	20 (95.2%)	21 (100%)	/	/	/
Locally advanced stage (III + IV) (n = 50)	6 (12.0%)	34 (68.0%)	40 (80.0%)	50 (100%)	/	/	/
Primary tumor location							
Hypopharynx (n = 25)	5 (20.0%)	20 (80.0%)	25 (100%)	25 (100%)	/	/	/
Larynx (n = 46)	7 (15.2%)	28 (60.9%)	35 (76.1%)	46 (100%)	/	/	/
Sequential therapy							
Surgery (n = 39)	1 (2.6%)	31 (79.5%)	32 (82.1%)	39 (100%)	37 (94.9)	8 (20.5)	52 (73.2%)
Radiotherapy (n = 24)	8 (33.3%)	13 (54.2%)	21 (87.5%)	24 (100%)	/	/	
T.C.M. (n = 2)	1 (50.0%)	1 (50.0%)	2 (100%)	2 (100%)	/	/	
Chemotherapy (n = 1)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	/	/	
No sequential therapy (n = 5)	2 (40.0%)	2 (40.0%)	4 (80.0%)	5 (100%)	/	/	

Note: [a]AJCC 8th edition, T.C.M.: Traditional Chinese medicine.

Following the study treatment, several patients underwent surgery (n = 39), radiotherapy (n = 24), traditional Chinese medicine (n = 2), and chemotherapy (n = 1). The R0 resection rate, pCR of 39 patients receiving sequential surgery were 94.9% (37/39), 20.5% (8/39), respectively. The larynx preservation rate was 73.2% (52/71), including 20 patients with larynx preservation surgery and 32 patients without surgery. Five patients did not perform any sequential therapy: 40% (2/5) reported a complete response, 40% (2/5) reported a partial response (Table 2).

3.3 Tumor Downstaging

The T downstaging in patients with hypopharyngeal and laryngeal cancer was 64.0% (16/65) and 50.0% (23/46), the N downstaging was 28.0% (7/25) and 2.2% (1/46) ($p = 0.001$), respectively. In patients at the early stage and locally advanced stage, the T downstaging was 66.7% (14/21) and 50.0% (25/50), the N downstaging was 0% (0/21) and 16.0% (8/50) ($p = 0.128$), respectively (Table 3).

Table 3: Downstaging

Category[a]	T downstaging n (%)	N downstaging n (%)	*p* value
Early stage (I + II) (n = 21)	14 (66.7%)	0 (0%)	0.128
Locally advanced stage (III + IV) (n = 50)	25 (50.0%)	8 (16.0%)	
Tumor location			
Hypopharynx (n = 25)	16 (64.0%)	7 (28.0%)	0.001
Larynx (n = 46)	23 (50.0%)	1 (2.2%)	

Note: [a]AJCC 8th edition.

3.4 Long-Term Survival

The median PFS was 29.2 months in the patients with laryngeal cancer (Fig. 1). The OS was not achieved in both groups (Fig. 2). In patients at the early stage, death and disease progression were 4.8% (1/21) and 14.3% (3/21), respectively. In patients at the locally advanced stage, death and disease progression were 12% (6/50) and 28% (14/50), respectively. In patients with hypopharyngeal cancer, death and disease progression were 12% (3/25) and 24% (6/25), respectively. In patients with laryngeal cancer, death and disease progression were 8.7% (4/46) and 23.9% (11/46), respectively (Fig. 3).

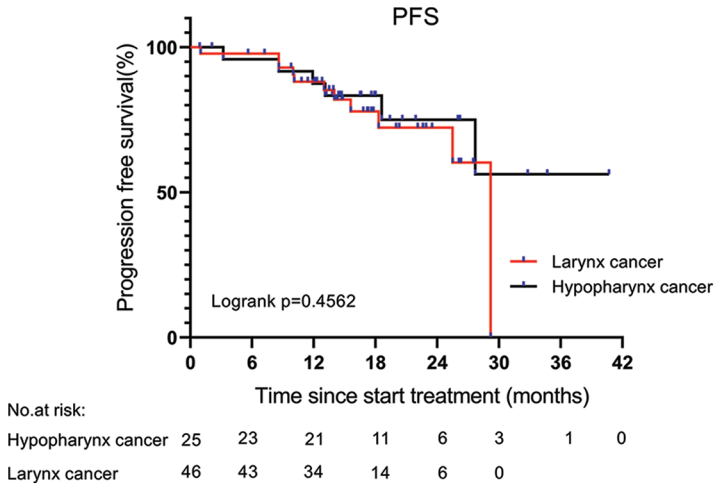

Figure 1: Kaplan-Meier estimate of PFS for patients in the hypopharynx and larynx cancer group

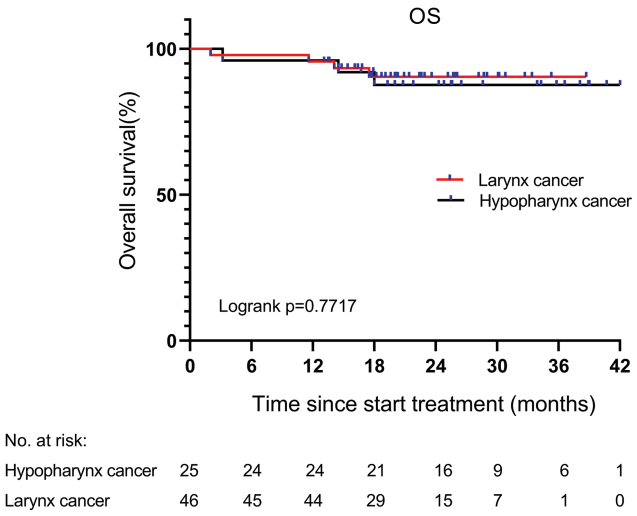

Figure 2: Kaplan-Meier estimate of OS for patients in the hypopharynx and larynx cancer group

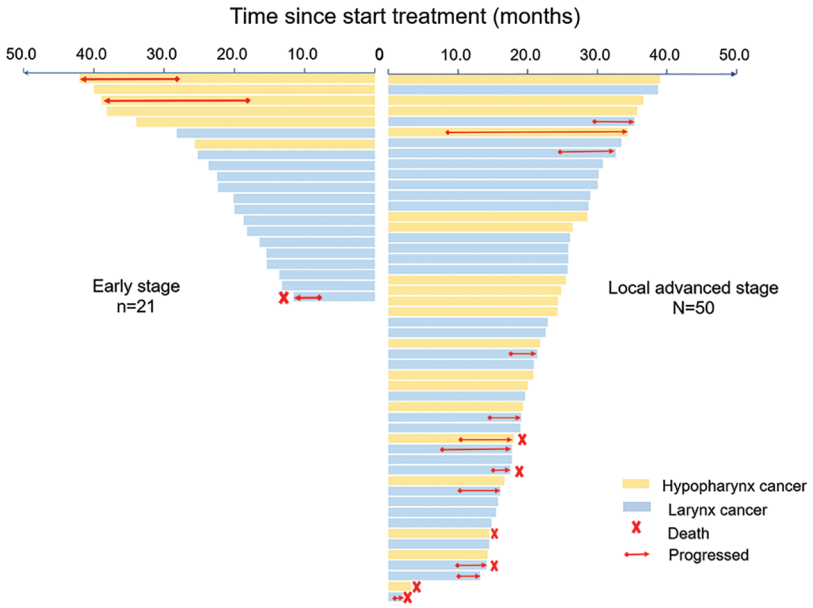

Figure 3: The OS and PFS events for patients in the early stage and local advanced stage group

3.5 Adverse Events

A total of 67 patients reported mild-to-moderate adverse events. The most common adverse events were bone marrow suppression (29.6%), electrolyte disorders (46.5%), and gastrointestinal reaction (45.1%). Grade 3 adverse events were documented, including bone marrow suppression (2.82%) and electrolyte disorders (2.82%). No grade 4 adverse events were encountered (Table 4).

Table 4: Adverse events

Adverse reaction	Grade 1	Grade 2	Grade 3
	n (%)		
Bone marrow suppression	11 (15.49%)	10 (14.08%)	2 (2.82%)
Electrolyte disorders	31 (43.66%)	2 (2.82%)	2 (2.82%)
Gastrointestinal reaction	28 (39.44%)	4 (5.63%)	0
Sore throat	3 (4.23%)	0	0
Anorexia	1 (1.41%)	0	0
Swelling of upper arm	1 (1.41%)	0	0
Rash	1 (1.41%)	0	0

4 Discussion

In this study, we administered nimotuzumab combined with chemotherapy in patients with hypopharyngeal or laryngeal cancer. The ORR in hypopharyngeal cancer *vs.* laryngeal cancer was 100% *vs.* 76.1%, at the early stage (I + II) group and local advanced stage (III + IV) was 95.2% *vs.* 80.0%, including 12 cases of complete response and 48 cases of partial response. Overall, 39 patients achieved a T downstaging and 8 patients achieved an N downstaging. The N downstaging was significantly different between hypopharyngeal and laryngeal cancer (28.0% *vs.* 2.2%, $p = 0.001$). No grade 4 adverse events occurred during the study. The TPF regimen (docetaxel, cisplatin, and 5-fluorouracil) is the standard induction chemotherapy regimen in locally advanced HNSCC. A phase III study compared the efficacy of TPF *vs.* PF (cisplatin and 5-fluorouracil) regimens in HNSCC patients, reporting that the ORR was 72% *vs.* 64% ($p = 0.07$) and the CRR was 17% *vs.* 15%. The incidence of grade 3 or 4 hematologic adverse events was high, including neutropenia (83% *vs.* 56%), anemia (12% *vs.* 9%) and thrombocytopenia (4% *vs.* 11%). The incidence of grades 3–4 non-hematologic toxicities was 65% in the TPF group and 62% in the PF group [25]. A retrospective analysis showed that the ORR was significantly increased (83%) in locally advanced or metastatic HNSCC patients receiving a modified TPF (cisplatin, 5-fluorouracil, docetaxel, and leucovorin). Two deaths (4%) occurred during chemotherapy and 10 patients (21%) discontinued the treatment due to adverse events. Febrile neutropenia and grades 3–4 diarrhea occurred during the first cycle of treatment in 2 patients (4%) and 3 patients (6%), respectively [26]. Komatsu et al. [27] retrospectively assessed the efficacy and safety of concurrent chemoradiotherapy with TPF in patients with locally advanced HNSCC, showing that the ORR was 98.6% and 96.4% in patients with primary tumors located in the larynx and hypopharynx, respectively. The most common adverse reaction was neutropenia. Grades 3–4 AEs occurred in 65.0% of patients. Grade 3 dermatitis and mucositis occurring in 60.0% of patients. Compared with previous TPF and PF regimens, the combination of nimotuzumab with induction chemotherapy achieved similar ORR scores without increasing the chemotherapeutic toxicity.

As previously demonstrated, nimotuzumab combined with radiotherapy, chemotherapy, or chemoradiotherapy significantly prolonged the survival of HNSCC patients. Rodríguez et al. [28] assessed the efficacy of nimotuzumab plus radiotherapy in 106 advanced HNSCC patients, showing that nimotuzumab significantly increased CRR (59.5% *vs.* 34.2%, $p = 0.028$) and mOS (12.50 months *vs.* 9.47 months, $p = 0.0491$). Reddy et al. [22]. found that nimotuzumab with concurrent chemoradiotherapy or radiotherapy was effective in patients with inoperable advanced HNSCC. The ORR was significantly higher in patients treated with nimotuzumab than those treated with chemoradiotherapy or radiotherapy alone (100% *vs.* 70%, $p = 0.020$; 76.47% *vs.* 36.84%, $p = 0.023$). During the 5-year follow-up, receiving chemoradiotherapy or radiotherapy

plus nimotuzumab was associated with a higher OS (49.38 months *vs.* 16.36 months, $p = 0.012$) in the patients and reduced the death risk by 48%. Similar findings have been observed in other studies combining nimotuzumab with cisplatin and radiotherapy [24,29].

The studies investigating nimotuzumab combined with induction chemotherapy or chemoradiotherapy in laryngeal and hypopharyngeal cancer are limited. A single-center study in China showed the ORR was significantly increased in patients with unresectable locally advanced hypopharyngeal cancer treated with nimotuzumab plus induction chemotherapy compared with patients treated with chemotherapy alone (91.7% *vs.* 58.3%, $p = 0.029$) [30]. The OS at two years was 62.5% *vs.* 51.8% ($p < 0.05$), and the PFS at two years was 23 months *vs.* 18 months, ($p < 0.05$). Wang et al. assessed the efficacy of nimotuzumab combined with TPF regimen for locally advanced HNSCC [31]. They showed that the PFS and OS rates at two years were 71.2% and 78.3%, respectively. The ORR was 87.1%. Rash and treatment-related deaths were not reported. Zhang et al. [32] found that an EGFR inhibitor combined with non-surgical therapy (induction chemotherapy with the TP regimen, concurrent chemoradiotherapy or concurrent radiotherapy) increased the laryngeal preservation rate in patients with hypopharyngeal carcinoma. The OS and laryngeal preservation rates at three years were 68.9% and 86.7%, respectively. In our study, the ORR in patients with hypopharyngeal and laryngeal cancer was satisfactory.

In conclusion, nimotuzumab plus chemotherapy achieved similar ORRs and downstaging rates compared with previous studies. However, this study is also affected by limitations. First, this is a single-center retrospective study with a relatively small sample size. Second, the long-term survival benefit was only simply analyzed because of short of OS and PFS events. The continued follow-up or an RCT study with a larger sample size focusing on long-term survival is needed.

5 Conclusion

Nimotuzumab combined with neoadjuvant or induction chemotherapy achieved similar short-term efficacy and less adverse events compared with previous studies. The N downstaging rate in patients with hypopharyngeal cancer was significantly higher compared with patients with laryngeal cancer.

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Ethics Approval and Informed Consent Statement: This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (reference: 2021229). Informed consent was obtained from all participants prior to enrollment.

Availability of Data and Materials: To gain date access, researchers need to email to corresponding author for obtaining individual participant data that underline the results reported in this article after deidentification.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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