A Long Survival of III-IVb Stage Nasopharyngeal Carcinoma Treated with IMRT with or without Nimotuzumab: a Propensity Score-matched Analysis

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Abstract

Backgrounds: To assess the efficacy of Nimotuzumab in combination with first-line treatment of chemoradiotherapy of Chinese patients with primary III-IVb stage nasopharyngeal carcinoma. Methods: Patients with primary locoregionally advanced nasopharyngeal carcinoma who were treated with intensity-modulated radiotherapy (IMRT) and concurrent Cisplatin-based chemotherapy between January, 2008 and December, 2013 at a single institution were retrospectively reviewed. Group A received at least 6 doses of Nimotuzumab; Group B did not received Nimotuzumab. A propensity score matching method was used to match patients from each group in a 1:3 ratio. Results: In total, 730 eligible patients were propensity-matched, with 184 patients in Group A and 546 in Group B. There were no significant differences in patient and tumor characteristics between Group A and Group B. At a median follow-up of 74.78 months (range 3.53–117.83 months), locoregional recurrence, distant failure and death were observed in 10.68%, 11.10% and 16.03% of all patients, respectively. Estimated 5-year locoregional relapse-free survival, distant metastasis-free survival, progression-free survival and overall survival in the Group A versus Group B were: 85.34% versus 89.79% (P=0.156), 93.09% versus 85.61% (P = 0.012), 79.96% versus 77.99% (P = 0.117) and 88.91% versus 78.30% (P=0.006), respectively. Conclusions: This nimotuzumab-containing regimen resulted in a better long-term survival in III-IVb stage NPC patients, and warrants further prospective evaluation.

Background

Nasopharyngeal carcinoma (NPC) is a cancer arising from the nasopharynx epithelium. Most new cases occurred in Southeast Asia and it is also endemic in southern China (1-3). Due to a large population and high morbidity of nasopharyngeal carcinoma( NPC) of South China(4), the number of NPC patients is huge and nearly 5000 NPC patients are diagnosed
in Sun Yat-sen University Cancer Centre each year. NPC is distinguished from other types of head and neck cancers due to its unique sensitivity to both radiotherapy and chemotherapy. The current management of loco-regionally advanced NPC is radiotherapy combined with cisplatin-based concurrent chemotherapy. With the development of modern radiation therapy techniques, the treatment outcomes has improved a lot during the past decades (5). However, we must realize that the treatment of NPC has entered a plateau period and need new strategy or method to improve.

EGFR is overexpressed in approximately 90% of squamous cell carcinomas of the head and neck (6-8). More than 80% of NPC patients is also overexpressing EGFR and its expression is associated with unfavourable T stage and overall survival (9, 10). With the development of molecular-targeted therapy, EGFR represents a promising therapeutic target in oncology for its correlation with aggressive phenotype, treatment resistance and poor prognosis. Nimotuzumab is a humanized anti-EGFR monoclonal antibody, which binds to the extracellular domain of the EGFR and inhibits EGF binding, designed to reduce immunoreactivity and to enhance radio sensitivity (11). Nimotuzumab has demonstrated a unique clinical safety profile (12), where anti-tumor activity was observed in absence of severe skin, renal, gastrointestinal mucosa toxicities commonly associated with EGFR-targeting antibodies(13). Previous clinical studies of nimotuzumab concurrent with radiotherapy in patients with locally advanced head and neck squamous cell carcinoma reported that the combination was well tolerated and may enhance the radio curability of unresectable head and neck neoplasms (14). In addition, the side effects of the introduce of Nimotuzumab to chemoradiotherapy were mild, and it did not affect the normal execution of radiotherapy (15).

In this study, we aimed to assess the efficacy of nimotuzumab combined with radiotherapy in patients with advanced nasopharyngeal carcinoma. The primary endpoint was the
evaluation of overall survival and progression-free survival.

Methods

Patients

The Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center (SYSUCC) approved this retrospective review. We reviewed the inpatient medical records of primary nasopharyngeal carcinoma patients treated with IMRT at SYSUCC between January 2008 and December 2013. A total of 6,908 patients were identified. The eligible patients met the following criteria including: (i) Patients stages III-IVb disease; (ii) Histologically proven nonmetastatic NPC; (iii) Karnofsky Performance Status (KPS) \( \geq 80 \); (iv) Completion of radical radiotherapy; (v) Without previous anti-cancer treatment. The exclusion criteria were as follows: (a) age is older than 70 years; (b) disease progression during radiotherapy; (c) pregnancy or lactation; (d) not receiving concurrent chemotherapy; (e) concurrent chemotherapy is not cisplatin based; (f) received other anti-EGFR targeting therapy, and (g) previous malignancy or other concomitant malignant disease. The staging workup included an MRI of the head and neck, a chest radiograph, a bone scintigraphy, and an ultrasonography of the abdominal region for all the patients. All the included patients were restaged according to the Seventh Edition of the American Joint Committee on Cancer (AJCC) staging system. From these criteria, 1,274 patients were selected for the matched study (Figure 1).

We performed an analysis of variance, as well as a \( \chi^2 \) test, on the patients’ baseline demographics and clinical characteristics. Variable differences were identified between the two groups, including gender, age, tumor stage (T stage) and node stage (N stage), clinical stage and chemotherapy regime, all of which were identified as prognostic factors for survival outcomes in a previous study. Using propensity scores to adjust for these
factors, we created a well-balanced cohort by matching each patient who underwent nimotuzumab with no more than three patients who underwent chemoradiotherapy without nimotuzumab (Table 1). From this stratification process, we selected a total of 730 patients comprised of 184 patients in the nimotuzumab arm and 546 patients in the no nimotuzumab arm (Table 1). We first conducted case-matched comparison between the two arms in terms of efficacy and safety in this well-balanced cohort of 730. Subsequently, we conducted univariable and multivariate analysis of those 730 patients.

**Treatment**

**Radiation Therapy**

All patients received IMRT. The primary nasopharyngeal gross tumor volume (GTVnx) and the involved cervical lymph nodes were determined based on the MRI/CT and/or PET-CT imaging, clinical, and endoscopic findings. The enlarged retropharyngeal nodes together with primary gross tumor volume (GTV) were outlined as the GTVnx on the IMRT plans. The clinical tumor volume (CTV) represents the primary tumor with potential sub-clinical disease. The first clinical tumor volume (CTV1) was defined as the GTV plus a 0.5-1.0 cm margin (0.2 to 0.3 margin posteriorly) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. Clinical target volume 2 (CTV2) was defined as the CTV1 plus a 0.5-1.0 cm margin (0.2 to 0.3 margin posteriorly) to encompass the low-risk sites of microscopic extension, the level of the lymph node, and the elective neck area (bilateral levels IIa, IIb, III, and Va are routinely covered for all N0 patients, whereas ipsilateral levels IV, Vb, or supraclavicular fossae were also included for N1-3 patients). The prescribed dose was 66–70 Gy to the planning target volume (PTV), 60 Gy to PTV1, 54 Gy to PTV2, and 60–66 Gy to PTV of the involved cervical lymph nodes in 28 to 33 fractions. All patients were treated once daily, five fractions weekly. Dose constrains to the critical structures were within the tolerance according to the RTOG 0225 protocol, and
efforts were made to meet the criteria as closely as possible.

**Chemotherapy**

During the study period, concurrent chemoradiotherapy (CCRT) ± induction chemotherapy (IC) for stage III to IV disease was recommended according to our institutional guidelines. The study-defined concurrent chemoradiotherapy regimen was 80–100mg/m2 cisplatin on day 1 every 3 weeks for 2–3 cycles or 30mg/m2 cisplatin weekly. Patients receiving other chemotherapy regimens or who received only one cycle of induction or concurrent chemotherapy were excluded from this study. The study-defined induction chemotherapy regimens included PF (n=161) (80-100 mg/m2 cisplatin on day 1 and 800 mg/m2 /d fluorouracil civ on days 1–5), TP (n=176)(75mg/m2 docetaxel on day 1 and 75 mg/m2 cisplatin on day 1 or TPF(142) (75mg/m2 docetaxel on day 1, 75 mg/m2 cisplatin on day 1 and 800 mg/m2 /d fluorouracil civ on days 1– 5); both regimens were repeated every 3 weeks for 2–3 cycles. Reasons for deviating from the institutional guidelines included organ dysfunction suggesting intolerance to chemotherapy, patient refusal, and the discretion of the doctors in individual cases.

**Nimotuzumab delivery**

Nimotuzumab was not recommended for NPC patients by the guideline at that time. So the uses of Nimotuzumab was determined by the patients’ willing and the experience of doctors. Intravenous Nimotuzumab was administered at an initial dose of 200mg weekly during whole radiation period. A total of 184 patients received full doses of Nimotuzumab.

**Follow-up**

Patient follow-up was measured from the first day of therapy to the day of last examination or death. Patients were examined at least every 3 months during the first 2 years, with follow-up examinations every 6 months for 3 years or until death. The last follow-up date was 20 April 2019.
Statistical analysis

Distant metastasis-free survival (DMFS) and locoregional relapse-free survival (LRRFS) were calculated from day 1 after completion of treatment to first distant metastasis and locoregional relapse, respectively; progression-free survival (PFS) was calculated from day 1 after completion of treatment to locoregional relapse, distant relapse or tumor-related death, whichever occurred first. Overall survival (OS) was calculated from day 1 after completion of treatment to last examination or death respectively.

The clinic-pathologic characteristics of participants are described, and the differences of these characteristics between the Nimotuzumab group and non-Nimotuzumab group were compared by $\chi^2$ test for categorical variables, and t-test for continuous variables. Logistic regression analysis was used to identify confounders between the treatment groups. A propensity score matching method was used. Propensity scores were calculated based on the identified potential confounders and other important factors such as tumor stage, and then each patient was assigned a score. Using 0.2-caliper width, 1:3 matching was performed between patients in the Nimotuzumab group and non- Nimotuzumab group based on the propensity scores.

LRRFS, DMFS, PFS and OS were calculated using the Kaplan-Meier method. The differences of LRRFS, DMFS, PFS and OS between two groups were tested using log-rank test. Multivariate analysis was performed using the Cox proportional hazards models. All statistical analysis was performed using SPSS 21.0 statistical software (Chicago, IL, USA). A $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Patient characteristics are detailed in Table 1. A total of 6908 consecutive NPC patients
who were treated with IMRT between January 2008 and December 2013 at SYSUCC were analysed, and 1274 patients were eligible for propensity score matching, as shown in Fig 1. Gender, age, T-category, N-category clinical stage and chemotherapy regime (IC alone, IC+CCRT) were used to generate a propensity score model (Figure 1).

Eventually, 730 patients were propensity matched in this study to create two groups: Group A includes 184 cases, which received Nimotuzumab; Group B includes 546 cases, which did not received Nimotuzumab. Among the 730 patients, 154 are female and 576 are male. All the 730 patients received cisplatin based concurrent chemotherapy, and 479 of them received two courses of induction chemotherapy. The characteristics of the patients were well balanced between the propensity-matched groups. The median dose delivered during the initial course of radiation was 70 Gy (range, 66 – 80 Gy).

Mean age at the time of reirradiation was 43.92 years (SD=10.53) for Group A and 44.12 years (SD=10.62) for Group B. At a median follow-up of 74.78 months (range 3.53–117.83 months), the 1, 3, 5-year follow-up rate were 99.6%, 96.7% and 90.5%.

**Efficacy**

At the median follow-up of 74.78 months (range 3.53–117.83 months), there were 117 (16.03%) deaths. At the time of the analysis, 68 (9.32%) had locoregional failure, 10 (1.34%) showed locoregional failure and distant metastases, and 71 (9.73%) developed distant metastases.

The 5-year DMFS, LRRFS, PFS and OS rates of group A and group B were 93.90% vs. 85.61% (p = 0.012) | 85.34% vs. 89.79% (p=0.156), 79.96% vs. 77.99% (p=0.117) and 96.33% vs. 85.97% (p = 0.006), respectively (Table 2). There was significantly difference in DMFS and OS between group A and Group B, but there was no difference in LRRFS and PFS. The 5-year DMFS, LRRFS, PFS and OS according clinical stage were done and there was only significantly difference in OS for stage III. The survival curves were shown in
Prognosis

The overall survival (OS) of 730 cases were analysed by univariate and multivariable cox regression models, respectively. We included sex, age, T stage, N stage, clinical stage, received nimotuzumab treatment or not and concurrent chemotherapy (with or without induction chemotherapy) in the model. The result showed that T stage, N stage, clinical stage and nimotuzumab or not were found to have prognostic significance in OS (Table 3). Multivariate analysis indicated that N stage and nimotuzumab treatment were the independent prognostic factors for DMFS and OS [Table 4]. The patients with advance N stage had a poorer prognosis and those received nimotuzumab had significantly better 5-year OS than those didn’t receive nimotuzumab (88.91% versus 78.30%, P < 0.01) [Table 2].

Discussion

In spite of the employment of cisplatin-based chemoradiotherapy, the treatment outcome for advanced stage is still unsatisfactory because of local recurrence and/or distant metastasis as the major pattern of disease failure (16). With modern radiation techniques and equipment, it enables to the delivery of high-dose of radiation to the target tissue while sparing normal organs at risk, thereby potentially enhancing the therapeutic efficacy (17). Previous studies have reported 90% local-regional control rates for nasopharyngeal carcinoma with the use of IMRT combined with systematic chemotherapy even in patients presenting with advanced loco-regional disease (18-20). As a consequence, distant metastasis plays an important role for the treatment failure and need to be managed properly and urgently. After decades of studies on chemotherapy for NPC, there is only slightly improve on survival and distant failure, so it is important to develop new treatment strategy to handle this issue which confuses clinical doctors for a
long term.

With further research of the molecular mechanism of tumorigenesis and tumor development, molecular targeted therapy in patients with NPC has become a research hotspot. As we now know that more than 90% patients with NPC were detected for over expression of EGFR(6, 7). EGFR is considered an important target in NPC treatment(21). Nimotuzumab which is a humanized anti-EGFR monoclonal antibody is obtained by replacing a murine complementary-determining region with a human framework. Nimotuzumab has shown high safety and low toxicity without severe skin and mucosa toxicities commonly associated with other EGFR targeting antibodies(12, 15). As reported, compared with other EGFR inhibitors, such as Cetuximab, nimotuzumab shows a greater advantage in terms of less toxicity(22). Another advantage of nimotuzumab is that the affinity constant is quite low, allowing for high tumor uptake and low normal tissues uptake. Research has showed that Nimotuzumab demonstrated marked antiproliferative, proapoptotic, and antiangiogenic effects in tumors that overexpress EGFR(23). Now, Nimotuzumab has been approved in several countries for the treatment of head and neck tumors(24, 25).

This current study retrospectively analysed the efficacy of 184 NPC patients received nimotuzumab plus IMRT/CCRT with or without induction chemotherapy. In our study, encouraging survival and distant metastasis control was attributed to the treatment with nimotuzumab. Our results showed promising clinical outcomes, with 5-year DMFS of 93.09%, 5-year LRRFS of 85.34%, 5-year PFS of 79.96%, and 5-year OS of 88.91%, comparing those didn’t receive nimotuzumab with 5-year DMFS of 85.61%, 5-year LRRFS of 89.79%, 5-year PFS of 77.99%, and 5-year OS of 78.30%. It seems reasonable that there was no observed significant difference in 5-year LRRFS (85.34% vs. 89.79%, $P = 0.156$) since IMRT provides excellent locoregional control(26). The current
analysis demonstrated that the adding of nimotuzumab, as opposed to CCRT alone, was associated with a significantly better OS, DMFS. There was significantly difference in DMFS (p=0.012) and OS (p=0.006). Further statistics showed that there is a significantly increase of OS in patients with stage III disease. These data indicated that the increase in survival outcome for NPC patients treated with nimotuzumab was mainly attributed to the significant increase in DMFS. The reason could be that nimotuzumab and cisplatin-based chemoradiotherapy would kill tumor cells to a greater extent, especially the cisplatin-based chemotherapy resistant micro-metastases.

Previous studies demonstrated that the main prognostic factors are age, gender, T, N category, clinical stage; the survival rate has been shown to decrease with the increasing T category and N category patients(27). According to our data, the multivariate analysis revealed that gender, N stage and nimotuzumab were significant prognostic factors for DMFS, N stage and nimotuzumab treatment were significant prognostic factors for OS, and node stage was a significant prognostic factor for PFS. Since only patients with clinical stage III and IV are included this study and the local-regional control rate is similar and no statistical significance (90.16% vs. 85.71%, p=0.156), this point can be explained by the use of modern radiation techniques which has been proved to improve local-regional control. While for distant failure, node stage still affects DMFS and OS as well, patients with advanced node stage have a higher chance to distant failure and lead to overall failure as a consequence. The results are consistent with other studies(5, 28). We must address that, after introduce a full course of nimotuzumab to NPC patients staged III to IV during chemoradiotherapy, there is a significant improve of overall survival with nearly 10% improve in OS significance (88.91% vs 78.30%, p=0.006). The results are encouraging and beyond our expectation. The strength of nimotuzumab combined with radiotherapy in NPC may be still largely due to a strengthening of the antitumor effect that nimotuzumab
and cisplatin-based chemoradiotherapy would kill tumor cells to a greater extent, which has been mentioned above.

But we must admit the limitations of this study and be cautious to interpreted the results since this study is a retrospective one. And the unavailability of the EGFR expression is another limitation since there were still a proportion of patients who were EGFR negative. Although we eliminated selection biases, such as gender, age, T and N stages, clinical stage using propensity scores, it is unclear whether other confounding factors still exist. In the future, some prospective, randomized, well-designed, and large sample clinical studies are needed to evaluate these indications.

Conclusions

In conclusion, our study observed that the administration of nimotuzumab to chemoradiotherapy in staged III-IV NPC patients showed promising clinic outcomes compared with chemoradiotherapy alone. However more studies, especially, prospective, well-designed, and large sample clinical studies are needed.

Abbreviations

IMRT: intensity-modulated radiotherapy
EGFR: epidermal growth factor receptor
University Cancer Center
KPS: Karnofsky Performance Status
Committee on Cancer
GTVnx: The primary nasopharyngeal gross tumor volume
PTV: planning target volume
MRI: Magnetic Resonance Imaging
NPC: Nasopharyngeal carcinoma
SYSUCC: Sun Yat-sen University Cancer Center
AJCC: American Joint Committee on Cancer
RTOG Radiation Therapy Oncology Group
chemoradiotherapy
IC induction chemotherapy
DMFS distant metastasis-free survival
LRRFS locoregional relapse-free survival
PFS progression-free survival
OS overall survival
CT computed tomography
PET-CT Positron emission tomography-computed tomography

Declarations

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Authors’ contributions
Chen Ming-Yuan and Hua Yi-Jun conceived the study. You Rui, Liu You-Ping and Sun Rui made substantial contributions to data acquisition, Wang Zhi-Qiang, Mei Qi and Li Ji-Bin analyzed the data and performed interpretation of data. Wang Zhi-Qiang, Mei Qi and Li Ji-Bin involved in drafting the manuscript. Hu Guang-Yuan and Hua Yi-Jun edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
This study complied with the standards of the Declaration of Helsinki and current ethical guidelines. It was approved by the Sun Yat-sen University Cancer Center research ethics committee. All patients provided written informed consent for the collection and
publication of their medical information at the first visit to our center, which was filed in their medical records.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no conflict of interest.

**Availability of data and materials**

The data of this research is deposited in RDD (http://www.researchdata.org.cn).

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Tables

Table 1. Baseline characteristics of patients with NPC treated with or without Nimotuzumab
| Characteristic            | Nimotuzumab Arm N = 184 | No Nimotuzumab Arm N = 546 | P    |
|--------------------------|-------------------------|----------------------------|------|
| Gender                   |                         |                            | 0.704|
| Female                   | 37(20.11)               | 117(21.43)                 |      |
| Male                     | 147(79.89)              | 429(78.57)                 |      |
| Age, Mean (SD)           | 43.92 (10.53)           | 44.1 2(10.62)              | 0.822|
| 44                       | 9551.63                 | 25346.34                   |      |
| ≥44                      | 8948.37                 | 29353.66                   |      |
| T classification         |                         |                            | 0.966|
| T1                       | 5(2.72)                 | 17(3.11)                   |      |
| T2                       | 16(8.70)                | 42(7.69)                   |      |
| T3                       | 107(58.16)              | 317(58.06)                 |      |
| T4                       | 56(30.42)               | 170(31.14)                 |      |
| N classification         |                         |                            | 0.972|
| No                       | 19(10.33)               | 57(10.44)                  |      |
| N1                       | 75(40.76)               | 230(42.13)                 |      |
| N2                       | 73(39.67)               | 214(39.19)                 |      |
| N3                       | 17(9.24)                | 45(8.24)                   |      |
| Clinical stage           |                         |                            | 0.937|
| III                      | 116(63.04)              | 346(63.37)                 |      |
| IVa                      | 51(27.72)               | 155(28.39)                 |      |
| IVb                      | 17(9.24)                | 45(8.24)                   |      |
| Chemotherapy             |                         |                            | 0.684|
| Concurrent               | 61(33.15)               | 190(34.80)                 |      |
| Induction + concurrent   | 123(66.85)              | 356(65.20)                 |      |

Table 2. 5-year survival rates of the 730 NPC patients
|       | All (n=730) | Nimotuzumab Arm (n=184) | NO Nimotuzumab Arm (n=546) | Chi square | P value |
|-------|-------------|-------------------------|---------------------------|------------|---------|
| DMFS  | 87.49%      | 93.09%                  | 85.61%                    | 6.343      | 0.012   |
|       | III         | 89.81%                  | 94.59%                    |            |         |
|       | IV          | 83.43%                  | 90.56%                    |            |         |
| LRRFS | 88.60%      | 85.34%                  | 89.79%                    | 2.012      | 0.156   |
|       | III         | 90.16%                  | 87.22%                    |            |         |
|       | IV          | 85.71%                  | 82.00%                    |            |         |
| PFS   | 78.47%      | 79.96%                  | 77.99%                    | 2.459      | 0.117   |
|       | III         | 78.72%                  | 81.27%                    |            |         |
|       | IV          | 63.15%                  | 70.90%                    |            |         |
| OS    | 80.96%      | 88.91%                  | 78.30%                    | 7.565      | 0.006   |
|       | III         | 88.53%                  | 96.33%                    |            |         |
|       | IV          | 67.69%                  | 76.24%                    |            |         |

OS: overall survival; DMFS: distant metastasis-free survival; LRRFS: locoregional relapse-free survival; PFS: Progression-free survival

Table 3. Prognostic factors associated with overall survival by Univariate cox regression models (N=730)
| Gender    | B   | SE  | HR(95%CI)   | P   | B   | SE  | HR(95%CI)   |
|-----------|-----|-----|-------------|-----|-----|-----|-------------|
| Female    | 1   |     |             |     | 1   |     |             |
| Male      | -0.943 | 0.372 | 0.3890.18 | 0.011 | 0.189 | 0.280 | 1.208(7-2.0) |

| Age       | B   | SE  | HR(95%CI)   | P   |
|-----------|-----|-----|-------------|-----|
| 44        | 1   |     |             |     |
| ≥44       | -0.106 | 0.223 | 0.9000.58 | 0.636 | -0.380 | 0.248 | 0.684(0-1.1:|

| Tumour stage | B   | SE  | HR(95%CI)   | P   |
|--------------|-----|-----|-------------|-----|
| T1           | 1   |     |             |     |
| T2           | 0.681 | 0.486 | 1.9750.76 | 0.161 | -0.145 | 0.736 | 0.865(4-3.6) |
| T3           | -0.213 | 0.450 | 0.8080.33 | 5-1.952 | 0.636 | 0.261 | 0.408 | 1.299(3-2.8) |
| T4           | -0.292 | 0.244 | 0.7470.46 | 3-1.205 | 0.232 | -0.373 | 0.267 | 0.689(8-1.1) |

| Node stage   | B   | SE  | HR(95%CI)   | P   |
|---------------|-----|-----|-------------|-----|
| N0            | 1   |     |             |     |
| N1            | -1.666 | 0.466 | 0.1890.07 | 0.000 | -1.554 | 0.667 | 0.211(7-1.0) |
| N2            | -1.960 | 0.325 | 0.1410.07 | 0.000 | -0.742 | 0.387 | 0.476(3-1.0) |
| N3            | -1.117 | 0.278 | 0.3270.19 | 0.000 | -0.472 | 0.380 | 0.624(6-1.3) |

| Clinical stage | B   | SE  | HR(95%CI)   | P   |
|---------------|-----|-----|-------------|-----|
| III           | 1   |     |             |     |
| IV            | -0.606 | 0.222 | 0.5460.35 | 3-0.844 | 0.006 | -0.405 | 0.244 | 0.667(3-1.0) |

| Target therapy | B   | SE  | HR(95%CI)   | P   |
|----------------|-----|-----|-------------|-----|
| Without        | 1   |     |             |     |
| With           | 0.796 | 0.325 | 2.2171.17 | 4-4.188 | 0.014 | -0.367 | 0.260 | 0.693(6-1.1) |

| Induction chemotherapy | B   | SE  | HR(95%CI)   | P   |
|------------------------|-----|-----|-------------|-----|
| No                     | 1   |     |             |     |
| Yes                    | 0.107 | 0.230 | 1.1130.70 | 9-1.747 | 0.642 | -0.354 | 0.270 | 0.702(3-1.1) |

Table 4. Multivariate analysis of variables correlated with the treatment regimen status and other significant prognostic factors in eligible 730 cases
|                  | Gender | DMFS | LRFS |                |                |
|------------------|--------|------|------|----------------|----------------|
|                  |        | B    | HR   | 95%CI          |                |
| Female           |        | 1    | 1    | 0.934          | 0.247          |
| Male             |        | -0.934| 0.393| 0.013          | 1.280          |
|                  |        |      |      | (0.188-0.823)  | (0.733-2.237)  |
|                  |        |      |      |                | 0.385          |
|                  |        |      |      |                | -0.205         |
|                  |        |      |      |                |                |
| Age              |        | 1    | 1    | 0.096          | -0.439         |
|                  |        |      |      | 0.909          | 0.645          |
|                  |        |      |      | (0.582-1.421)  | (0.393-1.058)  |
|                  |        |      |      | 0.675          | 0.082          |
|                  |        |      |      |                | -0.256         |
| Tumour stage     |        | 1    | 1    | 0.149          | -0.229         |
|                  |        |      |      | 1.161          | 0.795          |
|                  |        |      |      | (0.335-4.026)  | (0.113-5.603)  |
|                  |        |      |      | 0.814          | 0.818          |
|                  |        |      |      |                | -0.200         |
|                  |        |      |      |                |                |
|                  |        | 1    | 1    | -0.894         | 0.109          |
|                  |        |      |      | 0.409          | 1.116          |
|                  |        |      |      | (0.128-1.305)  | (0.246-5.065)  |
|                  |        |      |      | 0.131          | 0.887          |
|                  |        |      |      |                | -0.510         |
|                  |        |      |      |                |                |
|                  |        | 1    | 1    | -0.474         | -0.329         |
|                  |        |      |      | 0.623          | 0.720          |
|                  |        |      |      | (0.248-1.562)  | (0.175-2.954)  |
|                  |        |      |      | 0.313          | 0.648          |
|                  |        |      |      |                | -0.664         |
| Node stage       |        | 1    | 1    | -1.979         | -1.437         |
|                  |        |      |      | 0.138          | 0.238          |
|                  |        |      |      | <0.001         | 0.083          |
|                  |        |      |      | (0.046-0.418)  | (0.047-1.210)  |
|                  |        |      |      |                | -1.603         |
|                  |        |      |      |                |                |
|                  |        | 1    | 1    | -2.251         | -0.594         |
|                  |        |      |      | 0.105          | 0.552          |
|                  |        |      |      | <0.001         | 0.347          |
|                  |        |      |      | (0.043-0.260)  | (0.160-1.902)  |
|                  |        |      |      |                | -1.329         |
|                  |        |      |      |                |                |
|                  |        | 1    | 1    | -1.330         | -0.329         |
|                  |        |      |      | 0.264          | 0.720          |
|                  |        |      |      | (0.111-0.629)  | (0.204-2.542)  |
|                  |        |      |      | 0.003          | 0.609          |
|                  |        |      |      |                | -0.876         |
| Clinical stage   |        | 1    | 1    | 0.224          | -0.052         |
|                  |        |      |      | 1.251          | 0.950          |
|                  |        |      |      | 0.677          | 0.946          |
|                  |        |      |      | (0.436-3.593)  | (0.212-4.254)  |
|                  |        |      |      |                | 0.080          |
| Target therapy   |        | 1    | 1    | 0.840          | -0.339         |
|                  |        |      |      | 2.317          | 0.712          |
|                  |        |      |      | 0.010          | 0.194          |
|                  |        |      |      | (1.224-4.384)  | (0.427-1.189)  |
|                  |        |      |      |                | 0.353          |
| Induction        |        | 1    | 1    | 0.303          | -0.209         |
| chemotherapy     |        |      |      | 1.354          | 0.811          |
|                  |        |      |      | (0.849-2.159)  | (0.471-1.398)  |
|                  |        |      |      | 0.203          | 0.451          |
|                  |        |      |      |                | 0.031          |
Study flow diagram.
Figure 2

Kaplan-Meier plots of Distant metastasis-free survival, Locoregional relapse-free survival and Progression-free survival, Overall survival of NPC patients treated with (green lines) or without Nimotuzumab (blue lines) according clinical stage.