The Value of Cervical Node Features in Predicting Long-Term Survival of Nasopharyngeal Carcinoma in Intensity-Modulated Radiotherapy Era

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Research Article

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Abstract

The prognostic value of cervical node features in nasopharyngeal carcinoma (NPC) patients treated with intensity-modulated radiotherapy (IMRT) was controversial. In this study, about 1752 patients after IMRT from 2008 to 2011 were recruited. The nodal features including the nodal number, maximize dimension diameter, extranodal extension (ENE) and cervical node necrosis (CNN) were retrospective analyzed. Univariate Cox and multivariate proportional hazard regression models were used to test the prognostic value of nodal features. Prognostic nomograms were built to predict the survival. The 10-year distant metastases free survival (DMFS) and disease-specific survival (DSS) rates were 86.5% and 80.8%. By multivariate analysis, the independent factors for the DSS were gender, age, lactate dehydrogenase (LDH), CNN, ENE, T stage and N stage. Nomogram A (without nodal features) and nomogram B (with nodal features) were built. The calibration curve for the probability of DSS showed good agreement between prediction by nomogram and actual observation. The C-index of nomogram B was higher than for nomogram A in predicting DSS (0.708 vs 0.676, P <.01). These results demonstrated the nodal features including the ENE and CNN were negative prognostic factors in patients with NPC, and the prognostic nomogram incorporating the nodal features was more accurate.

Introduction

Nasopharyngeal carcinoma (NPC) is a unique head and neck malignancy with a distinct pattern of geographical distribution, which is common seen in Southeastern Asians. Because of the abundance of lymphatic drainage system in nasopharynx, 80%-90% NPC patients present with cervical node metastasis detected by the magnetic resonance imaging (MR) or computed tomography (CT). Furthermore cervical node metastasis is one of the most valuable prognosticator in predicting the high rate of distant metastasis and poor survival, and play a critical component in the TNM staging system. However, the N-classification is mainly determined by the parameters of size, level and laterality of the cervical node in the NPC stage system, the others potential valuable features are not included.

Accurate and comprehensive assessment of the metastatic cervical node is helpful to predict prognosis and evaluate the individual treatment options in NPC patients. There are now studies that suggest the nodal features including extranodal extension (ENE) and the number of node were strong prognostic factor of poor outcome in patients with HNSCC and were included in the 8th edition staging system. However the value of these nodal features in predicting long-term survival for the NPC patients in intensity-modulated radiation therapy (IMRT) era were relative limited and the results in some study were not consistent.

This study was to evaluate the prognostic value of the radiologic features of metastatic neck node for patients with NPC treated with IMRT and prognostic nomogram with the radiologic features was built to select the patients with high risk of treatment failure.

Methods And Materials
Materials

We retrospectively reviewed the patients with non-metastatic NPC between January 2008 and December 2011, and the inclusion criteria were: (1) pathologically-proven NPC, (2) with the cervical lymph node metastases(N+), (3) with complete imaging and clinical data, (4) treated with the full course of IMRT. Eventually, a total of 1753 NPC patients were enrolled in this study. All patients underwent the contrast-enhanced magnetic resonance imaging (MRI) of nasopharynx and neck in staging evaluation, and computed tomography scan (CT) and single photon emission computed tomography (SPECT) were used to exclude distant metastasis. Positron emission tomography (PET-CT) was also recommended when clinically indicated. Patients were re-staged according to the 7th edition AJCC staging system.

The protocol was in compliance with ethical standards and approved by the institutional ethics committee of Sun Yat-sen University Cancer Center. Written informed consent was obtained from all participants. All methods were performed in accordance with the relevant guidelines and regulations.

MRI image acquisition

MRI with a 1.5-T or 3.0-T system (SignaCV/i, General Electric Healthcare) was performed in all patients before treatment. The scanning area ranges from the suprasellar cistern to the superior border of the thoracic cage with a head and neck combined coil. Fast spin-echo (FSE) T1-weighted images (T1WIs) on the axial, sagittal, and coronal planes, and axial FSE T2-weighted images (T2WIs) were obtained before injection of contrast material. After intravenous injection of gadopentetate dimeglumine (Gd-DTPA, a dose of 0.1 mmol/kg body weight), axial and sagittal T1-weighted spin-echo and coronal T1-weighted fat-suppressed spin-echo images were sequentially obtained. The parameters for the T1WI and T2WI scan were TR = 500–600 ms and TE = 10–20 ms, and TR = 4000–6000 ms and TE = 95–110 ms, respectively. The thickness of MRI layers was 5 mm for the axial sequences and 2 mm for the coronal or sagittal sequences, with a 1-mm intersection gap.

MRI Assessment for the metastatic neck node

Metastatic neck node

Magnetic resonance images were interpreted by two radiation oncologists specialized in NPC with more than 10 years of experience; the disagreements were resolved by consensus of the team. The mainly diagnostic criteria for the metastatic node by the MR imaging was as follows: (1) the retropharyngeal lymph nodes with a minimal axial diameter of 5 mm, and other cervical lymph nodes with a minimal axial diameter of 10 mm; (2) groups of three or more lymph nodes in the same area with a minimal axial diameter of 8 mm; (3) lymph nodes of any size with extranodal extension (ENE) or central necrosis or enhancing rim. Besides with N classification, other radiologic features including the maximal axial diameter, number, extranodal extension and nodal necrosis were recorded.

Cervical Nodal necrosis (CNN)
The criteria for CNN was as a focal area of high signal intensity on T2-weighted images or low signal intensity on T1-weighted images, and non-enhancement on contrast-enhanced T1-weighted images (Figure-1).

**Radiologic extranodal extension (ENE)**

The criteria for rENE on MR images was as an unequivocal ill-defined border, mainly including the loss of sharp plane between the nodal capsule and the surrounding fat and the infiltration into surrounding structures (Figure-1).

**Radiotherapy and chemotherapy**

All patients were treated with the full course of intensity-modulated radiotherapy (IMRT). The target volume included gross tumor in nasopharynx (GTV-nx) and the involved cervical lymph nodes (GTV-nd), the high-risk clinical target volume (CTV1) and the low-risk clinical target volume (CTV2). A detailed description of IMRT including the delineation and prescription dose has been previously reported 16.

According to the institutional guidelines in the center, concurrent chemoradiotherapy was the main treatment for stage II-Iva/b disease; neoadjuvant or adjuvant chemotherapy was also administrated in patients with more advanced or bulky disease. Of the 1752 patients, 260 patients treated with radiotherapy alone and 1492 patients were treated with chemoradiotherapy. Concurrent chemoradiotherapy was administrated to 1195 patients, neoadjuvant chemotherapy was administrated to 776 patients and adjuvant chemotherapy was added to 96 patients.

**Follow-up and statistical analysis**

After the completion of treatment, patients were followed-up every 3 months during the first 2 years, every 6 months in 3-5 years, and then yearly thereafter until death.

The statistical analysis was performed with version 19.0 SPSS software. Kaplan–Meier method was used to calculated the local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), progress-free survival (PFS), overall survival (OS) and disease specific survival (DSS) rates. The log-rank test was used to compare the survival curves. Multivariate analysis with the Cox proportional hazards model was performed to test for independent prognostic factors. All statistical tests were two-sided, and P<0.05 was considered as statistically significant.

The nomogram was built based on the results of multivariate analysis using the package of rms in R version 2.10.1. The final prediction model was performed with a backward step down selection process with the Akaike information criterion. The performance of the nomogram was evaluated by concordance index (C-index) and assessed by comparing nomogram-predicted versus observed Kaplan-Meier estimates of survival probability 17,18. Comparison between the nomogram A (without ENE or CNN) and nomogram B (with ENE and CNN) was performed with the rcorr.cens package in Hmisc in R and were
evaluated by the C-index. The accuracy of the prognostic prediction was evaluated by the value of the C-index.

Results

Patient characteristics

The median age for the cohort was 44 years (range, 13–76 years), with the male (n=1279)-to-female (n=473) ratio of 2.7:1. The median maximal axial diameter was 19 mm (range: 5 mm–89 mm). The number of patients with N1, N2 and N3 were 837, 597 and 315 respectively. Furthermore, 768 patients were with ENE, and 825 patients were with rENE. The detail was shown in Table-1.

Survival and pattern of failure

The median follow-up for the whole was 124 months and 72 patients (4%) were lost to follow after 3- to 91-months. By the last follow-up date, distant metastasis occurred in 221 patients (12.6%) and became the most common pattern of failure. Among these with distant metastasis, 156 patients were with single organ metastasis and 65 patients were with multiple organs metastasis. The bone was the most common metastatic site, then was the lung and the liver. The 10-years DMFS rate was 86.5%.

A total of 161 patients developed local and/or regional failure including 119 patients with local failure only, 38 patients with regional failure only and 4 patients with both of them. The 10-years LRFS, RRFS and PFS rates were 92.6%, 97.4% and 78.6%, respectively.

A total of 347 patients died. Among these, 188 patients (188/347, 54.2%) died from the distant metastasis, 104 patients (104/347, 29.9%) died from the local +/- regional failure, 14 patients (14/347, 4.0%) died from radiation-related complications, 18 patients (18/347, 5.2%) died from other malignant tumors, 8 patients (8/347, 2.3%) died from the internal medication and 15 patients (15/347, 4.3%) died unknown causes. The 10-years OS and DSS rates were 79.8% and 80.8%. The detail was shown in Table-2.

Univariate and multivariate analysis

The results of univariate analysis show that the factors of LDH, the nodal number, CNN, rENE, T stage and clinical stage were identified as a significant prognostic factor for LRFS, DMFS, PFS and DSS, and N stage was also identified as a significant prognostic factor for DMFS, PFS and DSS (Table-1).

Consistent with the results of univariate analysis, multivariate analysis also show that the factors of CNN, rENE, T stage and N stage were significant prognostic factor for DMFS, PFS and DSS however the clinical stage and the nodal number were not independent prognostic factors. The 10-year DSS, DMFS and PFS for patients with CNN were poor than those without CNN, with 70.8% vs 88.6%, 80.8% vs 91.9%, 68.7% vs 86.2% (Figure-2). The 10-year DSS, DMFS and PFS for patients with rENE were also significantly poor than those without rENE, with 71.7% vs 86.7%, 79.8% vs 90.1%, 70.1% vs 86.0% (Figure-3).
The factors of T stage, LDH and CNN were associated with the LRFS, and the N stage and CNN were associated with the RRFS. The detail of the multivariate analysis was seen in Table-3.

**Establishment of nomograms model for DSS with or without nodal feature**

Firstly, we built a nomogram (Nomogram A) to predict the 5-, 10-year DSS rate only based on independent prognostic factors of gender, age, LDH, T stage and N stage. Then with the combinations of the ENE and CNN, a new nomogram (Nomogram B) was built to predict the 5-, 10-year DSS rate. Each variable has a corresponding score according to the point scale, and the total score is achieved by calculating the score of each variable. Next, by mapping the total score on the probability scale, the 5-, 10-year DSS rate probabilities could be estimated (Figure-4).

A calibration curve showed good agreement between prediction and observation in the probability of 5-, 10-year DSS. In Figure-5, the y-axes are observed DSS estimated by the Kaplan-Meier method, and the x-axes are predicted DSS calculated by the nomogram, and the solid lines represent the ideal reference line for which predicted survival corresponds with actual DSS. The C-index of nomogram B was 0.708 (95% CI = 0.681 to 0.733), which was higher than the C-index of nomogram A of 0.676 (95% CI = 0.649 to 0.703). The results indicated that nomogram B displayed better accuracy in predicting recurrence compared with Nomogram A.

**Discussion**

With the common application of IMRT in patients with NPC, the high rate of local control and reduced complications has been achieved in series of studies. In our previous study, the 10-year LRFS rate for patients treated with IMRT was up to 92%, significantly higher than those in the era of conventional RT. However, the incidence of distant metastasis was still up to 15-20%, and becoming the most common pattern of failure. The neck nodal metastasis has been demonstrated as the most important determinant of distant metastasis and poor survival. Therefore, the comprehensive evaluations of nodal morphological features might well help to select the patients with high risk of treatment failure. However, the AJCC N-classification of nodal disease was only based on the metastasis size, laterality and level, and other nodal features associated with treatment failure were not evaluated. In the present study, we found the nodal features including extranodal extension (ENE) and cervical nodal necrosis (CNN) were also associated with the poor survival and high risk of distant metastasis. The nomogram combined with the factors of nodal features displayed better accuracy in predicting survival compared with the nomogram without nodal features.

ENE had been demonstrated to be over-expression of some factors contributed to disease progression such as the matrix metalloproteinases and epidermal growth factor receptor gene (EGFR). For the factor of ENE was always associated with the high prone to the distant metastasis, it was considered as a critical parameter in upstaging the N classification in the new AJCC TNM stage system (8th ed., 2017) for non-viral related head and neck cancer. Furthermore, the factor of ENE after surgery was an
important indication for the intensive post-operative chemotherapy for patients with head and neck squamous cell cancer since the high risk of distant metastasis. In the study related to 266 tongue cancer, the 5-year OS rates were 75%, 50% and 30% for patients with N(-), N(+) with ENE (-), and N(+) with ENE(+) (p<0.01), the incidence of distant metastasis for patients with N(+) with ENE(+) was up to 52%. In the study of 258 patients with head neck squamous cell cancer, the 3-year OS and DMFS rates for patients with rENE(+) were only 64.3% and 72.3% (p<0.01), significantly lower than that of 82.8% and 90.6% in patients with rENE(-). However, the investigation of ENE was relative limited in patients with NPC for the surgery is not the primary treatment and no the pathological specimen is available. As the evidence showed the imaging technique of CT/MR exhibit the similar accuracy in the diagnosis of ENE compared with the pathological method. Several studies related to NPC has demonstrated that patients with ENE were associated with high risk of metastasis and poor outcome. In the report related to 1616 patients with NPC, the patients with rENE(+) had a significantly inferior 5-years DMFS (73.8% vs 88.4%, p < 0.01) and OS (77.3% vs 87.6%, p < 0.01) when compared to patients with rENE(-), and proposed to refine the N-classification according to the rENE. In a retrospective analysis of 1226 patients, Liu et al also show that rENE(+) was an independent prognostic factor for OS, but not for the PFS and DMFS. Similar to those study, we found that ENE was an negative independent factor for DMFS and OS. The 10-year DMFS and DSS for patients with ENE(+) were significantly poorer than those with ENE(-) (79.8% vs 86.7%, and 71.7% vs 89.1%, p<0.01).

Necrosis is also one of the valuable morphological features in the diagnosis of nodal metastasis, which is common in NPC patients with the incidence of 22-42%. Series studies demonstrated that the tumor necrosis was associated with the tumor hypoxia induced by the high tumor volume and the high speed of tumor growth. The presence of hypoxia in tumor exhibits poor sensitivity to chemoradiotherapy and accelerate progression during the treatment. Furthermore, studies have shown the association between the presence of CNN on CT and the poor survival after chemoradiotherapy in patients with head and neck cancer including NPC. Zoumalan et al reported that CNN at preoperative CT was a useful indicator of ENE and was an important negative prognostic indicator in patients with HNSCC. In the retrospective analysis related to 1800 NPC patients reporter by Lan et al, the 5-year OS and DMFS rates of the CNN and non-CNN groups were 78.8% vs 91.8%, and 78.4% vs 91.6%. The distant metastasis rate in the CNN group was up to 18.7%, significant higher than those without CNN with 4.6% (P<0.01). In a study reported by Liu et al, CNN on MRI was also demonstrated as a significant negative prognostic factor for OS, LRRFS and DMFS, patients with CNN had significantly inferior 5-year OS (82.6% vs. 87.8%), LRRFS (86% vs. 92.1%) and DMFS (81.6% vs. 89.5%) than those without CNN. Similar to those result, the present study also indicated the nodal necrosis was also associated with poor survival, the patients with CNN had more inferior 10-year DSS (70.8% vs 88.6%) and DMFS (80.8% vs 91.9%) than those without CNN.

Series nomograms based on the independent factors have been established to predict the survival in NPC patients and shown to be more accurate than the TNM staging systems, which is useful to select the patients with high risk of treatment failures. Patients with high risk of treatment failures may benefit from the more aggressive therapy. For patients with high risk of local recurrence, neoadjuvant
Chemotherapy was recommended by reducing tumor volume and improving the tumor control\textsuperscript{27}. Furthermore, adjuvant chemotherapy after radiotherapy may be administrated for patients with high risk of distant metastasis\textsuperscript{28}. However, most of the nomograms did not include the nodal features including the ENE and CNN. In the study, the nomogram combined with the factors of ENE and CNN displayed better accuracy in predicting 5-10 year DSS compared with the nomogram without the nodal features, which may be more appropriate in stratifying the patients with individual treatment.

There are some limitations in the present study. Firstly, this is a retrospective study related to the influence of nodal features on survival, some selection bias related to the treatment might influence the results. Secondly, for the diagnosis of ECS and CNN was based on the MRI, the accuracy of the early ENE and CNN may be poorer when compared with the histology. Thirdly, the prognostic nomogram was no external validation, future external validation with larger cohorts from other institutions was warranted to confirm.

In conclusion, the nodal features including the ECS and CNN were independent negative prognostic factors for the DSS and DMFS in patients with NPC, and the nomogram combined with the nodal features displayed better accuracy in predicting survival compared with the nomogram without nodal features.

Declarations

Author contributions

Conception and design: Fei Han, Li Bai and Yun-ming Tian. Provision of study materials or patients: Yun-ming Tian, Lei Zeng, Run-da Huang, Yu-hong Lan, Xia Yuan, Li Bai, Fei Han. Collection and assembly of data: All authors. Data analysis and interpretation: Yun-ming Tian, Li Bai, Fei Han. Manuscript writing: Yun-ming Tian, Li Bai, Fei Han. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

Competing interests

The authors declare no competing interests.

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Tables

Table-1 Characteristics of 1752 patients and univariate analysis
| Characteristics                          | No.  | 10y-LRFS (%) | P value | 10y-DMFS (%) | P value | 10y-DSS (%) | P value |
|-----------------------------------------|------|--------------|---------|--------------|---------|-------------|---------|
| Gender,                                 |      |              |         |              |         |             |         |
| Male                                    | 1279 | 93.8         | 0.13    | 85.8         | 0.01    | 78.7        | <0.01   |
| Female                                  | 473  | 90.7         | 0.01    | 91.7         | 0.001   | 86.2        |         |
| Age(year),                              |      |              |         |              |         |             |         |
| <45y                                     | 881  | 92.6         | 0.17    | 89.3         | 0.74    | 86.2        | 0.04    |
| ≥45y                                     | 871  | 90.4         | 0.01    | 86.4         | 0.001   | 78.9        |         |
| Comorbidity\(^1\)                       |      |              |         |              |         |             |         |
| Yes                                     | 362  | 91.8         | 0.73    | 88.6         | 0.82    | 79.7        | 0.88    |
| No                                      | 1390 | 90.4         | 0.01    | 87.8         | 0.05    | 81.2        |         |
| LDH(year),                              |      |              |         |              |         |             |         |
| ≤245                                    | 1634 | 92.0         | 0.02    | 88.3         | <0.01   | 82.0        | <0.01   |
| >245                                    | 107  | 83.1         | 0.01    | 74.5         | 0.001   | 61.9        |         |
| Maximal axial diameter(cm),             |      |              |         |              |         |             |         |
| ≤3.0                                    | 1394 | 91.7         | 0.87    | 89.1         | <0.01   | 83.0        | <0.01   |
| >3.0                                    | 358  | 91.5         | 0.01    | 79.5         | 0.001   | 715         |         |
| Number of node,                         |      |              |         |              |         |             |         |
| ≤3                                      | 937  | 93.4         | 0.03    | 91.3         | <0.01   | 86.0        | <0.01   |
| >3                                      | 915  | 88.3         | 0.01    | 80.0         | 0.001   | 70.9        |         |
| CNN                                     |      |              |         |              |         |             |         |
| Yes                                     | 768  | 88.7         | 0.01    | 80.8         | <0.01   | 70.8        | <0.01   |
| No                                      | 984  | 93.6         | 0.01    | 91.9         | 0.01    | 88.6        |         |
| ENE                                     |      |              |         |              |         |             |         |
| Yes                                     | 825  | 89.4         | 0.02    | 79.8         | <0.01   | 71.7        | <0.01   |
| No                                      | 927  | 93.5         | 0.01    | 90.1         | 0.01    | 86.7        |         |
| T stage                                 |      |              |         |              |         |             |         |
| T1                                      | 92   | 98.8         | <0.01   | 95.6         | <0.01   | 95.6        | <0.01   |
| T2                                      | 430  | 93.9         | <0.01   | 93.5         | <0.01   | 87.4        |         |
| T3  | 872 | 93.7 | 86.4 | 80.8 |
|-----|-----|------|------|------|
| T4  | 358 | 81.3 | 80.0 | 68.4 |

N stage

| N stage | Count | N1 | N2 | N3 |
|---------|-------|----|----|----|
| N1      |       | 837| 93.4| 0.91| 92.2| <0.01| 86.9| <0.01|
| N2      | 597   | 92.5| 87.9| 91.4| 0.91| 87.9| 81.0|
| N3      | 315   | 91.4| 71.8| 67.8| 63.7|

Clinical stage

| Clinical stage | Count | II | III | IVa+b |
|----------------|-------|----|-----|-------|
| II             | 264   | 94.9| <0.01| 96.4| <0.01| 93.0| <0.01|
| III            | 852   | 94.6| 90.5| 85.5 |
| IVa+b          | 836   | 85.7| 78.1| 69.1 |

Chemotherapy

| Chemotherapy | Count | Yes | No |
|--------------|-------|-----|----|
| Yes          | 1492  | 92.7| 91.3|
| No           | 260   | 92.1| 79.5|

Comorbidity mainly includes the hypertension, diabetes and other internal medications.

Table-2 Failure patterns in nasopharyngeal carcinoma (NPC) patients
Table-3 Multivariate analysis of prognostic factors

| Failure pattern          | ENE(+) (No.) | ENE(-) (No.) | P value | CNN(+) (No.) | CNN(-) (No.) | P value |
|--------------------------|--------------|--------------|---------|--------------|--------------|---------|
| Local-regional failure   |              |              |         |              |              |         |
| Local only               | 66           | 53           |         | 62           | 57           |         |
| Regional only            | 30           | 8            |         | 27           | 11           |         |
| Local+regional           | 2            | 2            |         | 3            | 1            |         |
| Total                    | 98           | 63           | 0.02    | 92           | 69           | 0.04    |
| Distant metastasis       |              |              |         |              |              |         |
| Bone only                | 43           | 22           |         | 53           | 12           |         |
| Lung only                | 30           | 20           |         | 31           | 19           |         |
| Liver only               | 26           | 9            |         | 22           | 13           |         |
| Other single organ       | 5            | 3            |         | 6            | 2            |         |
| Multiple organs          | 47           | 16           |         | 52           | 11           |         |
| Total                    | 151          | 70           | <0.01   | 164          | 57           | <0.01   |
| Cause of death           |              |              |         |              |              |         |
| Distant metastasis       | 140          | 53           |         | 136          | 57           |         |
| Local/regional failure   | 55           | 44           |         | 58           | 41           |         |
| Complications other cancers | 8          | 6            |         | 10           | 4            |         |
| Internal medication      | 10           | 8            |         | 12           | 6            |         |
| Unknown                  | 10           | 5            |         | 12           | 3            |         |
| Total                    | 229          | 118          | <0.01   | 232          | 115          | <0.01   |
| Variables | HR value | 95%CI | P value |
|-----------|---------|-------|---------|
| DSS,      |         |       |         |
| Age       | 1.47    | 1.20-1.80 | 0.01 |
| Gender    | 1.35    | 1.06-1.73 | <0.01 |
| LDH       | 1.64    | 1.19-2.24 | 0.01 |
| CNN       | 1.78    | 1.39-2.26 | <0.01 |
| ENE       | 1.43    | 1.10-1.85 | <0.01 |
| T stage   | 1.81    | 1.53-2.08 | 0.01 |
| N stage   | 1.42    | 1.23-1.63 | <0.01 |
| OS        |         |       |         |
| Age       | 1.62    | 1.33-1.97 | <0.01 |
| Gender    | 1.35    | 1.07-1.70 | 0.01 |
| LDH       | 1.58    | 1.16-2.15 | 0.01 |
| CNN       | 1.64    | 1.31-2.07 | <0.01 |
| ENE       | 1.33    | 1.05-1.70 | <0.01 |
| T stage   | 1.78    | 1.56-2.04 | 0.01 |
| N stage   | 1.41    | 1.24-1.62 | <0.01 |
| PFS       |         |       |         |
| Gender    | 1.52    | 1.17-1.96 | 0.01 |
| LDH       | 1.58    | 1.45-2.05 | 0.03 |
| CNN       | 1.71    | 1.33-2.17 | <0.01 |
| ENE       | 1.39    | 1.07-1.81 | <0.01 |
| T stage   | 1.60    | 1.39-1.84 | 0.01 |
| N stage   | 1.34    | 1.16-1.55 | <0.01 |
| DMFS      |         |       |         |
| Gender    | 1.60    | 1.13-2.26 | 0.01 |
| T stage   | 1.72    | 1.42-2.08 | <0.01 |
| N stage   | 1.62    | 1.34-1.96 | 0.01 |
| CNN       | 1.81    | 1.29-2.55 | <0.01 |
| ENE       | 1.60    | 1.11-2.30 | <0.01 |
|        |        |        |        |
|--------|--------|--------|--------|
|        | LRFS   |        |        |
| T stage| 2.05   | 1.62-2.68 | <0.01 |
| LDH    | 1.81   | 1.07-3.06 | 0.01  |
| CNN    | 1.57   | 1.62-2.20 | 0.01  |
|        | RRFS   |        |        |
| N stage| 1.58   | 1.12-2.51 | <0.01 |
| CNN    | 4.20   | 2.09-8.45 | <0.01 |