Lymph Node Ratio for Postoperative Staging of Laryngeal Squamous Cell Carcinoma with Lymph Node Metastasis

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Abstract

Background: Lymph node metastasis has a significant impact on laryngeal cancer prognosis. The role of lymph node ratio (LNR, ratio of metastatic to examined nodes) in the staging of laryngeal cancer was not reported.

Patients and Methods: Records of laryngeal cancer patients with lymph node involvement from Surveillance, Epidemiology, and End Results database (SEER, training set, N = 1963) and Fudan University Shanghai Cancer Center (FDSCC, validating set, N = 27) were analyzed for the prognostic value of LNR. Kaplan–Meier survival estimates, the Log-rank χ² test and Cox proportional hazards model were used for univariate and multivariate analysis. Optimal LNR cutoff points were identified by X-tile.

Results: Optimal LNR cutoff points classified patients into three risk groups R1 (≤ 0.09), R2 (0.09–0.20) and R3 (> 0.20), corresponding to 5-year cause-specific survival and overall survival in SEER patients of 55.1%, 40.2%, 28.8% and 43.1%, 31.5%, 21.8%, 2-year disease free survival and disease specific survival in FDSCC patients of 74.1%, 62.5%, 50.0%, and 67.7%, 43.2%, 25.0%, respectively. R3 stratified more high risk patients than N3 with the same survival rate, and R classification clearly separated N2 patients to 3 risk groups and N1 patients to 2 risk groups (R1–2 and R3).

Conclusions: R classification is a significant prognostic factor of laryngeal cancer and should be used as a complementary staging system of N classification.

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Introduction

As with other cancers of the head and neck, lymph node (LN) involvement decreases survival rates of laryngeal cancer by approximately 50%. [1] The treatment choice of laryngeal cancer depends on functional outcome, the patient’s wishes, reliability of follow-up, and general medical condition. For early-stage glottic or supraglottic cancers, surgery (partial laryngectomy through either endoscopic or open approaches) and radiotherapy seem to be equally effective. [1,2,3] For patients with T4a tumors, the standard approach is a total laryngectomy with ipsilateral thyroidectomy and neck dissection. [1] For managing other locally advanced, resectable glottic and supraglottic cancers, the NCCN guidelines recommended concurrent chemoradiation, surgery or induction chemotherapy as the primary care for individual choice. [1]

Postoperative radiation with or without concurrent chemotherapy were recommended by NCCN for patients with adverse features which included extracapsular nodal spread, positive margin, pT4 primary, N2 or N3 nodal disease, perineural invasion and vascular embolism. [1] Over the past 3 decades, more attention has been paid to the identification of factors that might help the surgeon to assess the precise risk of failure and benefit from more intensified therapy in individual patients. The lymph node ratio (LNR) was found to improve prognostic information in breast cancer, gastric cancer, colorectal cancer, melanoma and others. [4,5,6,7] Although the prevalence of overall metastasis and occult metastasis of lymph nodes were found for 40%–75% and 26%–36% of laryngeal cancer patients, there was still no report about LNR on the survival of laryngeal cancer. [8,9,10]

To discuss the role of LNR for the postoperative staging of laryngeal cancer, the SEER (Surveillance, Epidemiology and End Results)-registered laryngeal cancer patients with lymph node metastasis were analyzed and the cutoff points for the LNR in defining patients as high, medium or low risk groups were also identified in current study.

Patients and Methods

Patients

The SEER laryngeal cancer dataset was extracted from SEER database (SEER*Stat 7.0.5). [11] Cancers were limited to the
Larynx, which were defined as the glottis (C32.0, vocal cord), supraglottis (C32.1, false cord, posterior surface of epiglottis, aryepiglottic fold), subglottis (C32.2), laryngeal cartilage (C32.3), overlapping lesion of larynx (C32.8) and larynx, NOS (C32.9). Histology was limited to squamous cell carcinoma (histology code - broad groupings 8030–8090). Only laryngeal carcinomas as a single primary tumor or the first of two or more primary tumors were included. The LNR was calculated as the number of positive lymph nodes divided by the number of lymph nodes examined.

The cases with dis-concordant N classification information and the number of positive regional lymph nodes recorded in SEER database were rejected. Because the aim of current study was to identify the role of LNR staging for laryngeal cancer, the cases with unclassified T classification, M classification, grade and other variables were also enrolled in the analysis set and were defined as Tx, Mx and unknown group to avoid losing information and select bias. Finally, a total of 4183 cases of laryngeal carcinoma were collected as the analysis set, and among them 1963 cases had histology data from SEER. For FDSCC patients, written informed consent were obtained. The study was approved by the Review Board of Fudan University Shanghai Cancer Center, Shanghai, China.

Statistical Analysis

Firstly, we evaluated the prognostic value of LNR as a continuous variable, adjusting for other covariates associated with survival of 1963 SEER pN+ laryngeal cancer cases. Furtherly, we proceeded to determine the most appropriate cutoff points for categorizing LNR as high, medium, and low risk groups. Two pairs of cutoff points were identified using different methods and compared with LNR as a continuous variable to identify the optimal cutoff points. The first pair of cutoff points were identified by tertiles to split the patients into equal sized groups. [12,13] The second pair of cutoff points were calculated by X-tile using the optimal cutoff points. The first pair of cutoff points were identified by tertiles to split the patients into equal sized groups. [12,13] The second pair of cutoff points were calculated by X-tile using the optimal cutoff points. The first pair of cutoff points were identified by tertiles to split the patients into equal sized groups. [12,13] The second pair of cutoff points were identified by tertiles to split the patients into equal sized groups. [12,13] The second pair of cutoff points were calculated by X-tile using the optimal cutoff points.

Results

LNR is a Prognostic Factor of Laryngeal Cancer Survival

The clinical characteristics, 5-year cause specific survival (CSS) and overall survival (OS) estimates, and Log-rank $\chi^2$ test of univariate variables of the 1963 SEER patients with pN+ laryngeal cancer were shown in Table 1. Using multivariate Cox regression analysis, we found that race, radiation sequence, T classification, chemotherapy, and occult LNs metastasis, only patients primarily operated with neck dissection were enrolled in current research.

Cutoff Points Identification of LNR

To stratify the patients with lymph node metastasis as high, medium and low risk groups associated with CSS, the upper and lower tertiles of continuous LNR that corresponded to 0.06 and 0.23 were defined as the first pair of cutoff points. The $X$-tile, which can control the inflated type I error problem and minimize the loss of information due to multiple testing through cross-validation, identified 0.09/0.20 as the second pair of cutoff points. [6,14] The SEER cases with lymph node metastasis were stratified as high, medium and low risk groups according to the two pairs of cutoff points identified above. The case numbers, the 5-year CSS and 5-year OS of the different risk groups were summarized in Table 3. To compare the predictive ability of the categorical LNR and the continuous LNR, the $\chi^2$ and AIC value of the Cox regression model were analyzed to compare the predictive ability of the staging system. A smaller AIC value and a higher $\chi^2$ index value indicated a more desirable model for predicting outcome. A $P$ value of 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS software version 17.0 (SPSS Inc., Chicago, IL) and R 2.14.0 software with packages (MASS and Survival).

Selecting High Risk Patients by R classification

N classification was widely used for postoperative staging of lymph node of laryngeal cancer, while the cause specific survival curves of N3 crossed with N2 after 150 months follow-up (Figure 1A). N1, N2 and N3 accounted for 27.8%, 66.9% and 5.3% of all pN+ patients (Table 1). Compared with pN classification, the survival curves of individual R classification separated clearly even after 20 years follow-up (Figure 1C and 1D). The R classification also showed homogenous patients grouping which stratified the patients to 43.3% (R1), 23.3% (R2) and 32.9% (R3) of all pN+ patients (Table 3). The 5 and 10-year CSS and OS of N3 patients were and 31.9%, 22.7% and 20.6%, 11.1%, individually. The 5 and 10-year CSS and OS of R3 patients were and 28.6%, 19.8% and 21.8%, 12.0%, respectively. R3 stratified more high risk patients than N3 with the same survival rate.
Table 1. Clinicopathological characteristics, cause specific survival (CSS) and overall survival (OS) of SEER laryngeal cancer cases with pathological lymph node involvement.

| Categorical variables | No. of patients (n = 1963) | 5-year CSS Rate (%) | Log-rank $\chi^2$ | P value | 5-year OS Rate (%) | Log-rank $\chi^2$ | P value |
|-----------------------|---------------------------|----------------------|-------------------|--------|-------------------|-------------------|--------|
| Race                  |                           |                      |                   |        |                   |                   |        |
| White                 | 1480 (75.4%)              | 43.7                 | 3.965             | 0.138  | 33.9              | 5.289             | 0.071  |
| Black                 | 397 (20.2%)               | 38.8                 |                   |        | 29.7              |                   |        |
| Other                 | 86 (4.4%)                 | 48.1                 |                   |        | 40.9              |                   |        |
| Gender                |                           |                      |                   |        |                   |                   |        |
| Male                  | 1526 (77.7%)              | 42.1                 | 2.795             | 0.095  | 32.4              | 1.545             | 0.214  |
| Female                | 437 (22.3%)               | 45.9                 |                   |        | 36.8              |                   |        |
| Year of diagnosis     |                           |                      |                   |        |                   |                   |        |
| 1988–1994             | 429 (21.9%)               | 43.3                 | 0.390             | 0.823  | 33.1              | 0.228             | 0.892  |
| 1995–2001             | 637 (32.5%)               | 42.4                 |                   |        | 34.0              |                   |        |
| 2002–2008             | 897 (45.7%)               | 43.4                 |                   |        | 32.3              |                   |        |
| Primary site          |                           |                      |                   |        |                   |                   |        |
| Glottis               | 327 (16.7%)               | 40.9                 | 15.271            | 0.009  | 32.5              | 15.803            | 0.007  |
| Supraglottis          | 1285 (65.5%)              | 44.8                 |                   |        | 34.7              |                   |        |
| Subglottis            | 36 (1.8%)                 | 0                    |                   |        | 32.1              |                   |        |
| Laryngeal cartilage   | 11 (0.6%)                 | 32.7                 |                   |        | 24.2              |                   |        |
| Overlapping lesion    | 133 (6.8%)                | 41.0                 |                   |        | 29.6              |                   |        |
| Larynx, NOS           | 171 (8.7%)                | 36.0                 |                   |        | 28.7              |                   |        |
| Histological grade    |                           |                      |                   |        |                   |                   |        |
| I                     | 89 (4.5%)                 | 44.4                 | 17.037            | 0.002  | 21.628            | <0.001           |        |
| II                    | 937 (47.7%)               | 45.3                 |                   |        | 36.5              |                   |        |
| III                   | 783 (39.9%)               | 42.2                 |                   |        | 31.6              |                   |        |
| IV                    | 20 (1.0%)                 | 46.1                 |                   |        | 20.0              |                   |        |
| Unknown               | 134 (6.8%)                | 27.9                 |                   |        | 22.3              |                   |        |
| Radiation sequence    |                           |                      |                   |        |                   |                   |        |
| No radiation          | 504 (25.7%)               | 35.4                 | 33.328            | <0.001 | 56.831            | <0.001           |        |
| Pre-operative         | 72 (3.7%)                 | 38.3                 |                   |        | 28.9              |                   |        |
| Post-operative        | 1363 (69.4%)              | 45.9                 |                   |        | 37.2              |                   |        |
| Other                 | 24 (1.2%)                 | 38.3                 |                   |        | 27.3              |                   |        |
| Cancer directed surgery|                         |                      |                   |        |                   |                   |        |
| Yes                   | 1761 (89.7%)              | 44.5                 | 26.251            | <0.001 | 27.370            | <0.001           |        |
| Other                 | 202 (10.3%)               | 26.1                 |                   |        | 18.6              |                   |        |
| T staging             |                           |                      |                   |        |                   |                   |        |
| T1                    | 182 (9.3%)                | 57.7                 | 59.303            | <0.001 | 54.620            | <0.001           |        |
| T2                    | 526 (26.8%)               | 48.5                 |                   |        | 36.1              |                   |        |
| T3                    | 295 (15.0%)               | 42.1                 |                   |        | 34.7              |                   |        |
| T4a                   | 809 (41.2%)               | 39.3                 |                   |        | 31.2              |                   |        |
| T4b                   | 55 (2.8%)                 | 29.6                 |                   |        | 20.3              |                   |        |
| Tx                    | 96 (4.9%)                 | 24.5                 |                   |        | 17.6              |                   |        |
| N staging             |                           |                      |                   |        |                   |                   |        |
| N1                    | 546 (27.8%)               | 59.7                 | 61.415            | <0.001 | 47.574            | <0.001           |        |
| N2                    | 1313 (66.9%)              | 37.1                 |                   |        | 28.8              |                   |        |
| N3                    | 104 (5.3%)                | 31.9                 |                   |        | 20.6              |                   |        |
| M staging             |                           |                      |                   |        |                   |                   |        |
| M0                    | 1845 (94.0%)              | 44.1                 | 55.169            | <0.001 | 45.658            | <0.001           |        |
| M1                    | 89 (4.5%)                 | 19.2                 |                   |        | 15.4              |                   |        |
| Mx                    | 29 (1.5%)                 | 40.8                 |                   |        | 29.4              |                   |        |
R classification Stratify Individual N Patients to Different Risk Groups

To further analyze the role of R classification for stratifying patients to different risk groups, the R classification was defined for patients with individual N classification. For pN1 patients, the 5-year CSS and OS of R1 ($N=361$), R2 ($N=40$), R3 ($N=145$) groups were 65.3%, 67.0%, 43.5% (Log-rank $\chi^2$ 32.117, $P<0.001$) and 52.7%, 51.7%, 33.0% (Log-rank $\chi^2$ 27.654, $P<0.001$), respectively (Figure 2A and 2B). For pN2 patients, the 5-year CSS and OS of R1 ($N=468$), R2 ($N=400$), R3 ($N=445$) groups were 48.5%, 37.1%, 25.1% (Log-rank $\chi^2$ 63.523, $P<0.001$) and 37.6%, 29.6%, 18.9% (Log-rank $\chi^2$ 45.328, $P<0.001$), respectively (Figure 2C and 2D). No significant differences of CSS (Log-rank $\chi^2$ 5.493, $P=0.064$) and OS (Log-rank $\chi^2$ 2.713, $P=0.258$) were observed for individual R classification group of pN3 patients ($N=104$). R classification clearly separated N2 patients to 3 risk groups and N1 patients to 2 risk groups (R1–2 and R3). The survival of R1 patients of N2 classification is better than the survival of R3 patients of N1 classification. All these results supported that R classification can stratify the patients to different risk groups and complement N classification.

Validation of R Classification in FDSCC Patients

To validate R classification in the FDSCC patient set, 27 pN+ cases were analyzed and the median number of LNs examined, positive LNs and LNR were 38 (range, 8–123), 2 (range, 1–28) and 0.09 (range, 0.01–0.70), respectively. The 2-year DSS and DFS of R1 ($N=13$), R2 ($N=10$), R3 ($N=4$) patients were 74.1%, 62.5%,
Table 3. Univariate and multivariate analysis of the categorical and continuous LNR with cause-specific survival (CSS) and overall survival (OS) of SEER laryngeal cancer patients with lymph node metastasis.

| LNR classification | Case No. | 5-year CSS(%) | Log-rank \(x^2(P)\) | Multivariate analysis of CSS\(^1\) | 5-year OS(%) | Log-rank \(x^2(P)\) | Multivariate analysis of OS\(^1\) |
|--------------------|---------|----------------|---------------------|-------------------------------|-------------|---------------------|-------------------------------|
|                    |         |                |                     | HR (95% CI)   | C-index | AIC     | HR (95% CI)   | C-index | AIC     |
| Continuous LNR     |         |                |                     | 2.299(1.905–2.775) | 0.658 | 14037.85 | 1.810(1.532–2.138) | 0.642 | 18430.78 |
| Cutpoints 0.06/0.23 |         |                |                     | 0.658 | 14042.83 | 0.642 | 18432.54 |
| R1: 0–0.06         | 637     | 56.3           | (<0.001)            | Reference | 43.9 | (<0.001) | Reference |
| R2: 0.06–0.23      | 737     | 42.4           |                      | 1.270(1.074–1.502) | 33.4 | 1.233(1.070–1.421) |
| R3: >0.23          | 589     | 29.4           |                      | 1.928(1.635–2.273) | 22.2 | 1.624(1.409–1.871) |
| Cutpoints 0.09/0.20 |         |                |                     | 0.661 | 14027.14 | 0.645 | 18424.27 |
| R1: 0–0.09         | 860     | 55.1           | (<0.001)            | Reference | 43.1 | (<0.001) | Reference |
| R2: 0.09–0.20      | 458     | 40.2           |                      | 1.421(1.202–1.680) | 31.5 | 1.308(1.133–1.509) |
| R3: >0.20          | 645     | 28.8           |                      | 1.962(1.695–2.271) | 21.8 | 1.607(1.416–1.825) |

\(^1\)The multivariate analysis was adjusted using the same Cox regression model at Table 2.

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Figure 1. Kaplan–Meier survival estimates according to pN classification and R classification of SEER laryngeal cancer patients with lymph node metastasis: cause-specific survival (A) and overall survival (B) of the SEER set with different pN classification; cause-specific survival (C) and overall survival (D) of the SEER set with different R classification.

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50.0%, and 67.7%, 43.2%, 25.0%, respectively. The 2-year DSS and DFS of N1 ($N=5$) and N2 ($N=22$) patients were 50.0%, 69.5% and 50% and 47.6%, respectively. Although no statistical significance were found for survival difference of individual R classification and N classification due to less patients number, the R classification stratify patients to 3 risk groups clearly.

**Discussion**

When surgery was selected as the primary management of laryngeal cancer, more attention should be paid to identify factors that might help the surgeon to assess the precise risk of failure. The main prognosticators included T classification, quality of surgical resection, positive margins, two or more positive lymph nodes, largest node $\geq$ 3 centimeters in diameter, perineural invasion, and in some studies, age and gender. [15,16] In 2004, level I evidence was established for the postoperative chemoradiotherapy treatment of patients with selected high risk locally advanced head and neck cancers, with the publication of the results of two trials conducted in EROTC and RTOG. Extracapsular extension and/or microscopically involved surgical margins were the only risk factors for which the impact of chemotherapy enhanced radiation therapy was significant in both trials. [17] Our current results identified that lymph node ratio is as independent risk factors for the postoperative staging of laryngeal cancer. The R classification defined by the cutoff points 0.09/0.20 can clearly stratify patients to 3 risk groups clearly.

The significant decrease in the number of laryngeal cancer surgical cases and changing use of new drugs and radiation techniques in the chemoradiation era prevent a clear and accurate analysis of risks of postoperative failure based on single institution’s...
experience. SEER data are abstracted prospectively from registries comprising 26% of U.S. population, which is considered representative of the entire population, and the selection biases, recall biases, treatment fads, influence of loss to follow-up and other oversights associated with single institution’s research were managed [11,19]. Current studies use the largest series (SEER) of operated pN+ laryngeal cancer cases to analysis the role of R classification for staging of laryngeal cancer and validate the R classification in an independent dataset (FDSCC). The complementary data collection system and the cross-validation of SEER and FDSCC dataset reinforce the conclusion. While limitations still exist for current research, such as the inter-institution differences in patient management, unrecorded details of pathologic reports and medical management covariates of SEER dataset, the less patient number of FDSCC dataset. Integrating R classification with other risk factors to analysis the pooled data of inter-institutional clinical trials will achieve a definitive result of the postoperative staging of laryngeal cancer.

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In conclusion, we clearly identify that lymph node ratio was an independent prognostic factor of laryngeal cancer and R classification (LNR 0–0.09, LNR 0.09–0.20 and LNR >0.20) defines laryngeal cancer mortality adequately. R staging is a complementary staging system for N classification. R staging based stratification of patients for postoperative therapy and clinical trials deserved for further research.

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Author Contributions

Conceived and designed the experiments: YLW DSL YW ZYW QHJ. Performed the experiments: YLW. Analyzed the data: YLW DSL YW ZYW QHJ. Contributed reagents/materials/analysis tools: YLW DSL YW ZYW QHJ. Wrote the paper: YLW.