Nomograms for predicting survival outcomes in patients with primary tracheal tumors: a large population-based analysis

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Background: The aim of this study was to develop and validate reliable nomograms to predict individual overall survival (OS) and cancer-specific survival (CSS) for patients with primary tracheal tumors and further estimate the role of postoperative radiotherapy (PORT) for these entities.

Patients and methods: A total of 405 eligible patients diagnosed between 1988 and 2015 were selected from the Surveillance, Epidemiology, and End Results database. All of them were randomly divided into training (n=303) and validation (n=102) sets. For the purpose of establishing nomograms, the Akaike information criterion was employed to select significant prognostic factors in multivariate Cox regression models. Both internal and external validations of the nomograms were evaluated by Harrell’s concordance index (C-index) and calibration plots. Propensity score matching (PSM) method was performed to reduce the influence of selection bias between the PORT group and the non-PORT group.

Results: Two nomograms shared common variables including age at diagnosis, histology, N and M stages, tumor size, and treatment types, while gender was only incorporated in the CSS nomogram. The C-indices of OS and CSS nomograms were 0.817 and 0.813, displaying considerable predictive accuracy. The calibration curves indicated consistency between the nomograms and the actual observations. When the nomograms were applied to the validation set, the results remained reconcilable. Moreover, the nomograms showed superiority over the Bhattacharyya’s staging system with regard to the C-indices. After PSM, PORT was not associated with significantly better OS or CSS. Only squamous cell carcinoma (SCC) patients in the PORT group had improved OS compared to non-PORT group.

Conclusion: The first two nomograms for predicting survival in patients with primary tracheal tumors were proposed in the present study. PORT seems to improve the prognosis of SCC patients, which needs further exploration.

Keywords: nomogram, primary tracheal tumors, overall survival, cancer-specific survival, propensity score matching analysis

Introduction

Primary tracheal tumor, a rare disease, represents 0.5% of all malignancies.1 Several reports have estimated an incidence of ~0.9 new cases per 1,000,000 persons per year.2,3 Major histological subtypes include squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC).4 SCC was reported to be associated with men and smokers,5 while nonsmokers were more likely to suffer from ACC.6 Patients with tracheal tumors generally present symptoms such as cough and dyspnea. However, these signs are nonspecific, and most patients are misdiagnosed until advanced disease is detected through radiography or bronchoscopy.7 Although radical surgical resection
with negative margins has been suggested to be the optimal option for primary tracheal tumors, the resection rate is remarkably heterogeneous, and the five-year overall survival (OS) among these patients varies from 47% to 79% based on previous studies.8–10 However, treatment failure attributed to local recurrence and distant metastasis is not rare. According to several retrospective reports, patients with tracheal tumors appear to benefit from adjuvant therapy,11,12 but the roles of postoperative radiotherapy (PORT) and chemotherapy remain controversial.13–15 Moreover, considering the notably low incidence, there is no widely accepted staging system with sufficient predictive prognostic value for these neoplasms. Thus, the evaluation of tracheal tumors is neither accurate nor convenient for clinicians.

The current literature has shown the precise predictive value of nomograms in the management of other tumors, and they have been broadly implemented in clinical practice.16–18 In this study, we aimed to build a nomogram for patients diagnosed with primary tracheal tumors by using the data extracted from the Surveillance, Epidemiology, and End Results (SEER) database and further investigate the prognostic value of PORT by applying a propensity score matching (PSM) method.

**Materials and methods**

**Selection of study cohort**

We conducted this retrospective study using data retrieved from the SEER database (1973–2015), supported by the National Cancer Institute, which provides information regarding cancer patients in 18 registries of the US covering ~28% of the US population.19 We identified the primary tracheal tumors according to the primary site code C33.9, and the search was limited to the period from 1988 to 2015 (information on tumor size, nodal status, metastatic sites, and extent of disease were not collected in the database until 1988). Only patients who met the following criteria were included: 1) age above 18 years; 2) trachea as the first primary site; 3) survival time ≥1 month; and 4) cases with inadequate tumor data (tumor extension, lymph node status, and metastasis). Those with a death certificate or autopsy were excluded. A total of 405 eligible cases were identified and constituted the primary cohort of our study. To develop and validate the nomograms, the primary cohort was randomized into a training cohort (n=303) and validation cohort (n=102).

**Definition of tumor data**

Considering that there is no American Joint Committee on Cancer (AJCC) TNM staging system for tracheal tumors, we utilized the tumor features from the SEER database and categorized the patients according to the following classification: 1) Extension status: Extension 1 (E1), invasive tumor confined to trachea; E2, involving adjacent connective tissues (arch of aorta,azygos vein, right brachiocephalic vein, carotid sheath, common carotid artery, jugular arch, phrenic nerves, pretracheal fascia, recurrent laryngeal nerve, subclavian artery, and vagus nerve) or adjacent organs/structures (cricoid cartilage, esophagus, pleura, not otherwise specified: parietal and visceral; right and left main bronchi, sternum, thymus, thyroid gland, and vertebral column); E3, further contiguous extension; 2) Lymph node status: N0, no regional lymph node involved; N1, regional lymph nodes involved (mediastinal, paratracheal, and pretracheal); and 3) Metastatic status: M0, no metastatic site involved; M1, distant lymph node(s) only, organ metastasis other than distant lymph node(s), or distant metastasis plus distant lymph node(s). To properly estimate the prognostic value of tumor size in patients with tracheal tumor, the tumor size was stratified into two categories (cutoff point 3.9 cm) by using the X-tile program (version 3.6.1), which is a practical tool assisting marker cut point analysis according to the minimal P-value.

**Data collection**

Data extracted for each case included demographics (age at diagnosis, gender, race, marital status, and Contract Health Service Delivery Areas [CHSDA] region), tumor characteristics (as mentioned above), primary tumor treatment (surgery or radiation therapy), months of survival, cause-specific death classification, and vital status.

**Statistical analysis**

We employed Student’s t-test for continuous data. Categorical variables were evaluated using the chi-squared test or Fisher’s exact test. We used the OS (the interval from the date of initial anticancer treatment until the date of death or the last day of follow-up) and cancer-specific survival (CSS) (the time from the data of initial treatment until death from tracheal tumor) as the primary endpoints for comparison. Kaplan–Meier analysis and log-rank test were used for survival analysis. Univariate and multivariate survival analyses were conducted using the Cox proportional hazards model. Nomograms were constructed based on the significant prognostic factors of the multivariate Cox regression analyses. We used the backward step-down process based on Akaike information criterion (AIC) to finally recruit independent prognostic factors into the formulations of the nomograms. Both internal and external validations of the nomograms were conducted based on the training cohort and validation cohort. Calibration curves
of our nomograms were employed to determine whether the predicted survival and observed survival were in agreement, and the curves were corroborated with 1,000 resamples conducted for validation. We further assessed the performances of nomograms and a staging system proposed by Bhattacharyya by using the Harrell’s concordance index (C-index). The C-index ranges from 0.5 to 1.0, and a larger C-index shows better accuracy for predicting the prognosis. The comparison between the nomogram and the Bhattacharyya’s staging system was performed with the cccorr function in the Hmisc package in R. Recognizing that selection bias may influence the comparison of survival outcomes between patients who did or did not receive PORT, similar with previous study, a PSM analysis was conducted to reduce the potential differences among baseline characteristics between the two groups. The patients were matched on the basis of a greedy nearest neighbor algorithm with the caliper set at 0.1. The matching fixed ratio was 1:1. All statistical analyses were processed with R software version 3.4.2 (Institute for Statistics and Mathematics, Vienna, Austria; https://www.r-project.org/), and a two-side P-value <0.05 was considered to be statistically significant.

Results

Patient baseline characteristics

A total of 405 patients were identified with primary tracheal tumors, and the demographics and characteristics of the training cohort (303 patients) and validation cohort (102 patients) are detailed in Table 1. The majority of patients in both sets were of white ethnicity, male, married, and from the Pacific Coast and East regions. The most common histological

| Characteristic       | Training cohort (n=303) | Validation cohort (n=102) | P-value |
|----------------------|-------------------------|---------------------------|---------|
| Race (%)             | Black                   | 36 (11.9)                 | 12 (11.8) | 0.987 |
|                      | Others                  | 31 (10.2)                 | 11 (10.8) |         |
|                      | White                   | 236 (77.9)                | 79 (77.5) |         |
| Sex (%)              | Female                  | 134 (44.2)                | 46 (45.1) | 0.969 |
|                      | Male                    | 169 (55.8)                | 56 (54.9) |         |
| Year of diagnosis (%)| 1988–1999               | 59 (19.5)                 | 18 (17.6) | 0.801 |
|                      | 2000–2009               | 149 (49.2)                | 54 (52.9) |         |
|                      | 2010–2015               | 95 (31.4)                 | 30 (29.4) |         |
| CHSDA region (%)     | East                    | 106 (35.0)                | 36 (35.3) | 0.397 |
|                      | NP                      | 43 (14.2)                 | 19 (18.6) |         |
|                      | PC                      | 136 (44.9)                | 38 (37.3) |         |
|                      | SW                      | 18 (5.9)                  | 9 (8.8)   |         |
| Histology (%)        | ACC                     | 78 (25.7)                 | 31 (30.4) | 0.190 |
|                      | Others                  | 96 (31.7)                 | 38 (37.3) |         |
|                      | SCC                     | 129 (42.6)                | 33 (32.4) |         |
| Treatment (%)        | None                    | 33 (10.9)                 | 6 (5.9)   | 0.118 |
|                      | RT + surgery            | 113 (37.3)                | 39 (38.2) |         |
|                      | RT only                 | 102 (33.7)                | 29 (28.4) |         |
|                      | Surgery only            | 55 (18.2)                 | 28 (27.5) |         |
| E stage (%)          | E1                      | 155 (51.2)                | 59 (57.8) | 0.339 |
|                      | E2                      | 140 (46.2)                | 39 (38.2) |         |
|                      | E3                      | 8 (2.6)                   | 4 (3.9)   |         |
| N stage (%)          | N0                      | 214 (70.6)                | 80 (78.4) | 0.161 |
|                      | N1                      | 89 (29.4)                 | 22 (21.6) |         |
| M stage (%)          | M0                      | 268 (88.4)                | 94 (92.2) | 0.387 |
|                      | M1                      | 35 (11.6)                 | 8 (7.8)   |         |
| Tumor size (%)       | ≤3.9 cm                 | 158 (72.1)                | 51 (72.9) | 1.000 |
|                      | >3.9 cm                 | 61 (27.9)                 | 19 (27.1) |         |
|                      | Unknown                 | 84                       | 32        |         |
| Marital status (%)   | No                      | 130 (44.7)                | 43 (44.8) | 1.000 |
|                      | Yes                     | 161 (55.3)                | 53 (55.2) |         |
|                      | Unknown                 | 12                       | 6         |         |
| Age (mean (SD))      |                         | 59.58 (15.32)             | 58.81 (16.14) | 0.665 |

Notes: Others: carcinoids, mucoepidermoid carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous carcinoma. NRT: training cohort =7 and validation cohort =2; PORT: training cohort =106 and validation cohort =37.

Abbreviations: ACC, adenoid cystic carcinoma; CHSDA, Contract Health Service Delivery Areas; NP, Northern Plains; NRT, neoadjuvant radiotherapy; PC, Pacific Coast; PORT, postoperative radiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; SW, Southwest.
subtype was SCC. For both training and validation cohorts, most patients were classified in the E1, N0, and M0 stages and received either surgery or radiotherapy.

Table 2 summarizes the characteristics of the primary cohort across histological subtypes. SCC was primarily associated with elderly males, while ACC was more likely found in younger female patients. Compared to ACC and other histologies, patients with SCC also more likely experienced node metastasis and distant metastasis, and were more likely to have undergone radiotherapy. However, among patients who received both radiotherapy and surgery, ACC was the predominant subtype.

Univariate and multivariate Cox regression of the training cohort

For the training cohort, univariate analyses were performed to identify clinical variables that were significantly associated with OS and CSS. As shown in Table 3, age, race, gender, histological subtypes, treatment types, E, N, and M stages, and tumor size were significantly associated with OS. Regarding CSS, race lost its significance, while other variables continued to be significant parameters.

In the multivariate analysis, all of the original variables were initially entered into the Cox regression model. To determine the independent prognostic factors in this cohort, which could be adopted into the nomograms, we used the least value of AIC to select variables consistent with previous study.25 Age, marital status, histological subtypes, treatment, N stage, M stage, and tumor size were identified as prognostic factors for OS. Regarding CSS, marital status was excluded, while gender became significant indicator. The results of multivariate Cox regression are demonstrated in Table 4.

### Table 2 Clinopathological characteristics of primary tracheal patients in each histologic group

| Characteristic | SCC (n=162) | ACC (n=109) | Others† (n=134) | P-value |
|----------------|-------------|-------------|-----------------|---------|
| **Race (%)**   |             |             |                 |         |
| White          | 133 (82.1)  | 80 (73.4)   | 102 (76.1)      | 0.002   |
| Black          | 22 (13.6)   | 8 (7.3)     | 18 (13.4)       |         |
| Others         | 7 (4.3)     | 21 (19.3)   | 14 (10.4)       |         |
| **Sex (%)**    |             |             |                 |         |
| Female         | 58 (35.8)   | 63 (57.8)   | 59 (44.0)       | 0.002   |
| Male           | 104 (64.2)  | 46 (42.2)   | 75 (56.0)       |         |
| **Year of diagnosis (%)** |         |             |                 |         |
| 1988–1999      | 31 (19.1)   | 17 (15.6)   | 29 (21.6)       | 0.231   |
| 2000–2009      | 86 (53.1)   | 49 (45.0)   | 68 (50.7)       |         |
| 2010–2015      | 45 (27.8)   | 43 (39.4)   | 37 (27.6)       |         |
| **CHSDA region (%)** |         |             |                 |         |
| East           | 70 (43.2)   | 29 (26.6)   | 43 (32.1)       | 0.028   |
| NP             | 23 (14.2)   | 13 (11.9)   | 26 (19.4)       |         |
| PC             | 57 (35.2)   | 59 (54.1)   | 58 (43.3)       |         |
| SW             | 12 (7.4)    | 8 (7.3)     | 7 (5.2)         |         |
| **Treatment (%)** |         |             |                 |         |
| None           | 17 (10.5)   | 3 (2.8)     | 19 (14.2)       | <0.001  |
| RT + surgery† | 53 (32.7)   | 66 (60.6)   | 33 (24.6)       |         |
| RT only        | 76 (46.9)   | 18 (16.5)   | 37 (27.6)       |         |
| Surgery only   | 16 (9.9)    | 22 (20.2)   | 45 (33.6)       |         |
| **E stage (%)** |             |             |                 |         |
| E1             | 70 (43.2)   | 59 (54.1)   | 85 (63.4)       | 0.001   |
| E2             | 82 (50.6)   | 50 (45.9)   | 47 (35.1)       |         |
| E3             | 10 (6.2)    | 0 (0.0)     | 2 (1.5)         |         |
| **N stage (%)** |             |             |                 |         |
| N0             | 100 (61.7)  | 96 (88.1)   | 98 (73.1)       | <0.001  |
| N1             | 62 (38.3)   | 13 (11.9)   | 36 (26.9)       |         |
| **M stage (%)** |             |             |                 |         |
| M0             | 142 (87.7)  | 102 (93.6)  | 118 (88.1)      | 0.249   |
| M1             | 20 (12.3)   | 7 (6.4)     | 16 (11.9)       |         |
| **Tumor size (%)** |         |             |                 |         |
| ≤3.9 cm       | 68 (65.4)   | 71 (78.9)   | 70 (73.7)       | 0.104   |
| >3.9 cm       | 36 (34.6)   | 19 (21.1)   | 25 (26.3)       |         |
| Unknown        | 58          | 19          | 39              |         |
| **Marital status (%)** |       |             |                 |         |
| No             | 79 (51.3)   | 39 (36.8)   | 55 (43.3)       | 0.162   |
| Yes            | 75 (48.7)   | 67 (63.2)   | 72 (56.7)       |         |
| Unknown        | 8           | 3           | 7               |         |
| **Age, mean (SD)** |       |             |                 | <0.001  |

Notes: *Others: carcinoids, mucoepidermoid carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous carcinoma. *NRT: SCC =5, ACC =3, and Others =1; PORT: SCC =48, ACC =63, and Others =32.

Abbreviations: ACC, adenoid cystic carcinoma; CHSDA, Contract Health Service Delivery Areas; NP, Northern Plains; NRT, neoadjuvant radiotherapy; PC, Pacific Coast; PORT, postoperative radiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; SW, Southwest.
Role of nomograms in primary tracheal tumors

Construction of nomogram for OS and CSS

Nomograms for predicting 1- and 5-year OS (Figure 1A) and CSS (Figure 1B) were constructed by using the covariates mentioned above, and score details of each nomogram predictor are shown in Table 5. By adding the scores of all the selected variables, the probabilities of survival of the individual patients could be accurately determined.

Validation of the nomograms

The C-indices of the nomograms to predict OS were 0.813 (95% CI: 0.764–0.862) and 0.838 (95% CI: 0.748–0.927) for the training and validation cohorts, respectively, exhibiting excellent consistency with actual OS. Similarly, when the training and validation cohorts were applied to the nomogram for CSS, the C-index values were also greater than 0.7 (0.817 and 0.863, respectively). As shown in Figure 2, both

### Table 3 Univariate analysis of clinical characteristics for OS and CSS in primary tracheal patients in the training cohort

| Characteristics      | OS (HR, 95% CI) | P-value | CSS (HR, 95% CI) | P-value |
|----------------------|-----------------|---------|-----------------|---------|
| **Race**             |                 |         |                 |         |
| White                | Reference       | 0.034   | Reference       | 0.071   |
| Black                | 1.150 (0.740–1.770) | 0.541   | 1.040 (0.640–1.690) | 0.877 |
| Others               | 0.480 (0.270–0.870) | 0.016   | 0.560 (0.310–1.030) | 0.060 |
| **Sex**              |                 |         |                 |         |
| Female               | Reference       | 0.025   | Reference       | 0.012   |
| Male                 | 1.420 (1.040–1.930) | 0.225   | 1.530 (1.100–2.130) | 0.576 |
| **CHSDA region**     |                 |         |                 |         |
| East                 | Reference       | 0.013   | Reference       | 0.014   |
| NP                   | 1.000 (0.640–1.550) | 0.997   | 0.930 (0.580–1.510) | 0.780 |
| PC                   | 0.740 (0.530–1.040) | 0.082   | 0.720 (0.500–1.040) | 0.081 |
| SW                   | 0.620 (0.290–1.360) | 0.236   | 0.720 (0.330–1.580) | 0.409 |
| **Histology**        |                 |         |                 |         |
| SCC                  | Reference       | <0.001  | Reference       | <0.001  |
| ACC                  | 0.190 (0.120–0.310) | <0.001  | 0.210 (0.120–0.350) | <0.001  |
| Others               | 0.670 (0.480–0.930) | 0.017   | 0.690 (0.480–0.980) | 0.036 |
| **Treatment**        |                 |         |                 |         |
| None                 | Reference       | 0.012   | Reference       | 0.013   |
| RT + surgery         | 0.270 (0.160–0.440) | <0.001  | 0.280 (0.170–0.460) | <0.001  |
| RT only              | 0.800 (0.510–1.270) | 0.349   | 0.760 (0.470–1.230) | 0.264 |
| Surgery only         | 0.150 (0.080–0.290) | <0.001  | 0.130 (0.060–0.270) | <0.001  |
| **E stage**          |                 |         |                 |         |
| E1                   | Reference       | 0.005   | 1.650 (1.190–2.280) | 0.002  |
| E3                   | Reference       | 0.001   | Reference       | 0.001   |
| **N stage**          |                 |         |                 |         |
| N0                   | Reference       | <0.001  | 3.610 (2.580–5.050) | <0.001  |
| N1                   | 3.190 (2.320–4.390) | <0.001  | Reference       | <0.001  |
| **M stage**          |                 |         |                 |         |
| M0                   | Reference       | <0.001  | 3.530 (2.260–5.500) | <0.001  |
| M1                   | 3.270 (2.120–5.030) | <0.001  | Reference       | <0.001  |
| **Tumor size (cm)**  |                 |         |                 |         |
| ≤3.9                 | Reference       | <0.001  | Reference       | <0.001  |
| >3.9                 | 2.470 (1.660–3.680) | <0.001  | 2.580 (1.700–3.930) | <0.001  |
| Unknown              | 2.760 (1.960–3.890) | <0.001  | 2.690 (1.860–3.900) | <0.001  |
| **Marital status**   |                 |         |                 |         |
| Yes                  | 0.790 (0.580–1.070) | 0.131   | 0.770 (0.550–1.070) | 0.115 |
| Unknown              | 1.700 (0.820–3.520) | 0.157   | 1.390 (0.600–3.210) | 0.442 |
| Age                  | 1.050 (1.040–1.060) | <0.001  | 1.050 (1.030–1.060) | <0.001  |

**Notes:** E3 stage were too few to calculate accurately. RT + surgery: NRT =7 and PORT =105.

**Abbreviations:** CHSDA, Contract Health Service Delivery Areas; CSS, cancer-specific survival; NP, Northern Plains; NRT, neoadjuvant radiotherapy; OS, overall survival; PC, Pacific Coast; PORT, postoperative radiotherapy; RT, radiotherapy; SW, Southwest.
Table 4 Multivariate analysis of clinical characteristics for OS and CSS in primary tracheal patients in the training cohort

| Characteristics | OS                      | P-value | CSS                      | P-value |
|-----------------|-------------------------|---------|--------------------------|---------|
|                 | Full                    | AIC-based |                        |         |
| Race            |                         |          |                         |         |
| White           | Reference               | 0.355    | Reference               | 0.217   |
| Black           | 1.250 (0.770–2.020)     | 0.361    | –                        | –       |
| Others          | 0.990 (0.510–1.910)     | 0.979    | –                        | –       |
| Sex             |                         |          |                         |         |
| Female          | Reference               | 0.296    | Reference               | 0.073   |
| Male            | 1.140 (0.800–1.630)     | 0.467    | –                        | –       |
| CHSDA region    |                         |          |                         |         |
| East            | Reference               | 0.296    | Reference               | 0.073   |
| NP              | 1.180 (0.740–1.900)     | 0.489    | –                        | –       |
| PC              | 1.070 (0.730–1.560)     | 0.723    | –                        | –       |
| SW              | 0.920 (0.390–2.170)     | 0.846    | –                        | –       |
| Histology       |                         |          |                         |         |
| SCC             | Reference               | 0.296    | Reference               | 0.073   |
| ACC             | 0.360 (0.210–0.630)     | <0.001   | 0.340 (0.210–0.580)     | <0.001  |
| Others          | 1.050 (0.740–1.510)     | 0.773    | 1.050 (0.740–1.500)     | 0.779   |
| Treatment       |                         |          |                         |         |
| None            | Reference               | 0.296    | Reference               | 0.073   |
| RT + surgery    | 0.700 (0.390–1.260)     | 0.236    | 0.670 (0.390–1.170)     | 0.159   |
| RT only         | 0.940 (0.560–1.580)     | 0.828    | 0.920 (0.560–1.500)     | 0.728   |
| Surgery only    | 0.400 (0.190–0.810)     | 0.012    | 0.350 (0.180–0.690)     | 0.003   |
| E stage         |                         |          |                         |         |
| E1              | Reference               | 0.296    | Reference               | 0.073   |
| E2              | 1.170 (0.840–1.640)     | 0.348    | –                        | –       |
| E3              | –                      | –        | –                        | –       |
| N stage         |                         |          |                         |         |
| N0              | Reference               | 0.296    | Reference               | 0.073   |
| N1              | 1.950 (1.370–2.770)     | <0.001   | 1.970 (1.390–2.790)     | <0.001  |
| M stage         |                         |          |                         |         |
| M0              | Reference               | 0.296    | Reference               | 0.073   |
| M1              | 1.940 (1.210–3.120)     | 0.006    | 1.880 (1.190–2.980)     | 0.007   |
| Tumor size      |                         |          |                         |         |
| ≤3.9 cm         | Reference               | 0.296    | Reference               | 0.073   |
| >3.9 cm         | 1.800 (1.150–2.820)     | 0.010    | 1.770 (1.160–2.710)     | 0.009   |
| Unknown         | 2.120 (1.430–3.140)     | <0.001   | 2.080 (1.430–3.020)     | <0.001  |
internal and external calibration curves for 1- and 5-year OS and CSS suggested strong agreement between the prediction by nomogram and the actual outcomes in the training and validation cohorts.

We further compared the OS/CSS predictive ability between the nomogram and Bhattacharyya’s staging system. As shown in Table 6, the C-indices of the nomograms were significantly higher than those of the Bhattacharyya’s staging system for both OS and CSS (C-index: OS 0.810 vs. 0.660, \( P < 0.001 \); CSS 0.820 vs. 0.700, \( P < 0.001 \)).

**Value of PORT for tracheal patients**

For the purpose of evaluating the prognostic value of PORT comprehensively, a PSM analysis was conducted between patients who received surgical resection, either with or without PORT, based on age, race, gender, CHSDA region, histological subtypes, E, N, and M stages, tumor size, and marital status. Ultimately, 76 patients with PORT and 76 patients without PORT were enrolled in the matching cohort (Table S1). In the matching cohort, there was no significant difference regarding clinical characteristics, and neither OS nor CSS were significantly different between the two groups. In the subgroup analysis, PORT was not associated with superior outcome for ACC (figures not shown). Patients with SCC who received PORT had significantly better prognoses compared with those who did not, though only for OS (5-year OS: 61.5% vs 23.0%, \( P < 0.05 \); Figure S1).

**Discussion**

Due to the extremely low incidence of primary tracheal tumors, neither an AJCC staging system nor a reliable guideline for the management of these uncommon neoplasms has been established. Previously published investigations were primarily composed of case reports, reviews, and single-institutional experience.\(^1,3,7,26\) No large-scale study regarding the prognostic factors of tracheal tumors has been reported. As the graphical depictions of statistical models, nomograms have been used to predict individual survival outcomes among patients with other diseases.\(^{27-29}\) Because a multitude of advantages have been suggested, prognostic nomograms are widely accepted in clinical practice. By using the SEER dataset, we build two novel, user-friendly, and accurate nomograms for predicting the overall and disease-specific survival for patients with primary tracheal tumors. To the best of our knowledge, this study is the first to develop clinicopathological prediction models based on a large series of patients for this unique condition. Both internal and external validations of our nomograms showed effective discrimination.
that elderly patients always had worse survival than younger patients. Prior studies focused on other malignancies also suggested that diagnosis was highly significant for both OS and CSS. As expected, the effect of age characteristics, as well as patient status, to build comprehensive nomograms for tracheal neoplasm patients. Our study identified several clinicopathological characteristics as important prognostic factors for OS and CSS among patients with tracheal tumors. As expected, the effect of age at diagnosis was highly significant for both OS and CSS, and was included in our nomograms. Patients with SCCs at diagnosis had inferior outcomes than those with ACCs, with 5- and 10-year OS rates for SCCs of 79.0% and 62.3%, respectively, compared to 25.8% and 15.6% for ACCs, respectively (figures not shown). Our finding was consistent with those of previous studies. Gaissert et al\(^6\) compared the survival outcomes between these two groups. In ACCs, early detection has also been reported to associate with increased resectability rates and even improved survival.\(^6\) Another interesting finding was that females had better CSS than males. We noted that females were more likely to suffer from ACCs, while SCCs were more common among males. The survival difference among males compared to females could partly be explained by the different tumor biology behavior between ACCs and SCCs. Wang et al\(^2\) reported that consultation rates were significantly different between men and women, with men being more likely to endure symptoms for a long period and thus develop advanced disease with a less favorable prognosis, which could also be one explanation for the present study. Moreover, married patients had superior OS than their unmarried competitors. One explanation for this could be the difference in health-care seeking behavior between married and unmarried patients.\(^3\)\(^,\)\(^4\)

In our analysis, histological type was an important issue for both OS and CSS, and was included in our nomograms. Patients with SCCs at diagnosis had inferior outcomes than those with ACCs, with 5- and 10-year OS rates for ACCs of 79.0% and 62.3%, respectively, compared to 25.8% and 15.6% for SCCs, respectively (figures not shown). Our finding was consistent with those of previous studies. Gaissert et al\(^6\) compared the survival outcomes between 101 patients with ACCs and 90 patients with SCCs and found that the prognosis of ACCs was significantly superior to SCCs (5-year OS 52% vs. 39%, \(P<0.001\)). Another study based on oriental populations\(^5\) also suggested an approximately twofold 5-year survival rate disparity between these two subtypes.

Figure 1 Nomograms for predicting (A) 1- and 5-year OS and (B) CSS of primary tracheal tumors.
In our study, SCCs were more likely to present with local extension, as well as lymph node metastasis, than ACCs at diagnosis. Our study, together with published reports, might indicate different genetic alterations and tumor biology in different histological subgroups; however, further studies are warranted to evaluate this issue.

The presence of lymph node metastasis was found to be a poor prognostic indicator in our study, which has also been supported by a previous epidemiological study. For distant metastasis, our study innovatively classified nonregional node metastasis and distant organ metastasis as M1, which was consequently incorporated into the nomograms via the AIC-based selections. According to a prior study reviewing their 40 years of experience with treatment of ACC and SCC, Gaissert et al observed distant metastasis in 10% of diagnoses. Because the information of site-specific metastases was not collected until 2010, we further analyzed the metastatic patterns of tracheal tumor patients by querying the SEER database from 2010 through 2015. Among 125 eligible patients, the most frequent metastatic site was lung (16 patients, 12.8%) followed by liver (7 patients, 5.6%). The incidences of bone and brain metastases were 3.2% and 1.6%, respectively. In 1996, Maziak et al evaluated the proportion of metachronous metastases in 17 patients, which was in keeping with our findings. However, our study recruited a larger cohort and demonstrated the patterns of site-specific metastasis in primary tracheal malignancies for the first time.

It is not a surprise to find that the tumor extension was not an independent prognostic indicator for OS and CSS in our study. In fact, the size and location of the primary tumor have been reported to be more important than the extension of tumors. Another serial study also suggested that more advanced tumor extension might not correlate with higher mortality risk. Referring to the prognostic value of tumor size, our study selected 3.9 cm as the cutoff point, which was similar with Macchiarini’s study. Simultaneously, the AIC-based analyses demonstrated that those with tumor size <3.9 cm were associated with better prognosis.

Complete surgical resection with negative margins (R0 resection) has always been considered to be the mainstay strategy for tracheal tumors. Our study revealed that patients who underwent surgery had better survival outcomes compared to nonsurgery patients. However, due to the nature of the SEER database, details of surgical margins were lacking. Further large-scale studies examining the value of R0 resection compared to R1, and even R2, resection is needed. The role of PORT remains controversial. Few reports suggested that PORT seems to be effective for R1/R2 resected disease. However, these two studies are limited by small sample size and were less likely to provide sufficient information to determine the prognostic value of PORT. Xie et al conducted a population-based study to investigate this issue but did not separate PORT from neoadjuvant radiotherapy. Honings et al even drew a contradictory conclusion. To adjust for potential selection bias, we used the PSM method and evaluated the survival benefit from PORT in patients who received surgery: the favorable impact of PORT was only found for distant metastasis.
SCC patients. However, this should be taken cautiously due to the fact that the sample size was relatively limited and was from subgroup analysis. Previous studies have suggested lower radiosensitivity for ACC while neutron radiotherapy seems to improve the local-regional control for this condition.\textsuperscript{41} In contrast, Schraube et al\textsuperscript{42} and Jeremic et al\textsuperscript{11} noted significantly improved survival among SCC patients who underwent radiotherapy. Conversely, Yang et al\textsuperscript{6} suggested that ACC patients with R1 resection showed improved disease free survival of PORT but not in terms of OS. Our study, together with previous studies, suggested that the exact role of PORT in influencing survival remains unclear.

Several inevitable limitations in our study should be considered. First, as mentioned above, information on tumor location, surgical margins, techniques, prescription dose as well as fraction times of radiotherapy could not be ascertained from SEER. Second, prior studies evaluating the role of chemotherapy in the treatment of tracheal tumors have generated mixed conclusions. However, we could not examine this issue due to the lack of chemotherapy information in the SEER database. Finally, the database also lacks recurrence, performance status, and laboratory and pathological parameters, which could be used to build a more comprehensive nomogram.

Despite the abovementioned limitations, as well as the rarity of primary tracheal malignancies, our study created and validated the first two nomograms based on the combination of both anatomic and non-anatomic parameters, including clinical and epidemiological features, by using a large population-based approach. PORT seems to improve the prognosis of SCC patients, which warrants further investigation.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{(Continued)}
\end{figure}
Role of nomograms in primary tracheal tumors

Acknowledgments
This study was based on the publicly available SEER database, and permission was received from the National Cancer Institute to access the database for the purposes of research (the private SEER ID 13499-Nov2016). As this research did not include interaction with humans or use personal identifying information, informed consent was not required. We thank the American Journal Experts (https://www.aje.com/) for editing this manuscript.

Table 6 Comparison of nomograms with Bhattacharyya’s staging system

| Models                        | OS C-index (95% CI) | P-value | CSS C-index (95% CI) | P-value |
|-------------------------------|---------------------|---------|----------------------|---------|
| Nomogram (Model 1)            | 0.810 (0.770–0.852) | –       | 0.820 (0.750–0.897)  | –       |
| Bhattacharyya stage (Model 2) | 0.660 (0.600–0.710) | <0.001  | 0.700 (0.640–0.760)  | <0.001  |
| Model 1 vs. Model 2           | –                   | –       | –                    | –       |

Abbreviations: CSS, cancer-specific survival; C-index, Harrell’s concordance index; OS, overall survival.

Figure 2 Calibration curves of (A and C) 1- and 5-year OS and (E and G) CSS for training cohort, and (B and D) OS and (F and H) CSS for validation cohort.
Disclosure
The authors report no conflicts of interest in this work.

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## Supplementary material

### Table S1 Patient characteristics according to the administration of PORT before and after PSM

| Characteristics         | Before PSM | After PSM | P-value  | Before PSM | After PSM | P-value  |
|-------------------------|------------|-----------|----------|------------|-----------|----------|
|                         | PORT(−) (n=83) | PORT(+) (n=143) |          | PORT(−) (n=76) | PORT(+) (n=76) |          |
| Race (%)                | White 65 (78.3) | 108 (75.5) | 0.621 | 62 (81.6) | 58 (76.3) | 0.726 |
|                         | Black 7 (8.4) | 18 (12.6) |          | 6 (7.9) | 8 (10.5) |          |
|                         | Others 11 (13.3) | 17 (11.9) |          | 8 (10.5) | 10 (13.2) |          |
| Sex (%)                 | Female 44 (53.0) | 70 (49.0) | 0.652 | 40 (52.6) | 39 (51.3) | 1.000 |
|                         | Male 39 (47.0) | 73 (51.0) |          | 36 (47.4) | 37 (48.7) |          |
| Year of diagnosis (%)   | 1988–1999 16 (19.3) | 34 (23.8) | 0.719 | 16 (21.1) | 16 (21.1) | 0.655 |
|                         | 2000–2009 41 (49.4) | 65 (45.5) |          | 36 (47.4) | 31 (40.8) |          |
|                         | 2010–2015 26 (31.3) | 44 (30.8) |          | 24 (31.6) | 29 (38.2) |          |
| CHSDA region (%)        | East 23 (27.7) | 42 (29.4) | 0.696 | 19 (25.0) | 20 (26.3) | 0.725 |
|                         | NP 12 (14.5) | 24 (16.8) |          | 38 (50.0) | 33 (43.4) |          |
|                         | PC 40 (48.2) | 69 (48.3) |          | 12 (15.8) | 17 (22.4) |          |
|                         | SW 8 (9.6) | 8 (5.6) |          | 7 (9.2) | 6 (7.9) |          |
| Histology (%)           | SCC 16 (19.3) | 48 (33.6) | <0.001 | 16 (21.1) | 14 (18.4) | 0.056 |
|                         | ACC 22 (26.5) | 63 (44.1) |          | 22 (28.9) | 36 (47.4) |          |
|                         | Others 45 (54.2) | 32 (22.4) |          | 38 (50.0) | 26 (34.2) |          |
| E stage (%)             | E1 59 (71.1) | 74 (51.7) | 0.013 | 52 (68.4) | 49 (64.5) | 0.731 |
|                         | E2 24 (28.9) | 67 (46.9) |          | 24 (31.6) | 27 (35.5) |          |
|                         | E3 0 (0.0) | 2 (1.4) |          | 0 | 0 |          |
| N stage (%)             | N0 78 (94.0) | 111 (77.6) | 0.003 | 71 (93.4) | 69 (90.8) | 0.764 |
|                         | N1 5 (6.0) | 32 (22.4) |          | 5 (6.6) | 7 (9.2) |          |
| M stage (%)             | M0 78 (94.0) | 134 (93.7) | 1.000 | 72 (94.7) | 70 (92.1) | 0.744 |
|                         | M1 5 (6.0) | 9 (6.3) |          | 4 (5.3) | 6 (7.9) |          |
| Tumor size (%)          | ≤3.9 cm 51 (75.0) | 99 (66.1) | 0.092 | 47 (74.6) | 52 (83.9) | 0.271 |
|                         | >3.9 cm 17 (25.0) | 16 (13.9) |          | 16 (25.4) | 10 (16.1) |          |
| Marital status (%)      | No 40 (50.6) | 50 (36.0) | 0.049 | 39 (53.4) | 42 (58.3) | 0.617 |
|                         | Yes 39 (49.4) | 89 (64.0) |          | 34 (46.6) | 30 (41.7) |          |
| Age (mean [SD])         | 55.07 (19.66) | 56.41 (14.42) | 0.559 | 55.75 (19.14) | 56.41 (15.22) | 0.815 |

**Abbreviations:** ACC, adenoid cystic carcinoma; CHSDA, Contract Health Service Delivery Area; NP, Northern Plains; PC, Pacific Coast; PORT, postoperative radiotherapy; PSM, propensity score matching; SCC, squamous cell carcinoma; SW, Southwest.
Figure S1 OS for sCC tracheal patients who underwent PORT or not in the matched cohort.
Abbreviations: OS, overall survival; PORT, postoperative radiotherapy; sCC, squamous cell carcinoma.