Postoperative Nomogram for predicting Cancer-Specific and Overall Survival Among Patients with Medullary Thyroid Cancer

Li Chen  
Tianjin Medical University General Hospital

Yizeng Wang  
Tianjin Medical University General Hospital

Ke Zhao  
Tianjin Medical University General Hospital

Yuyun Wang  
Tianjin Medical University General Hospital

Dongyang Li  
Tianjin Medical University General Hospital

Xianghui He (hexh88@tmu.edu.cn)  
Tianjin Medical University General Hospital  https://orcid.org/0000-0001-9977-162X

Research article

Keywords: Nomograms, Medullary thyroid carcinoma, Cancer-Specific Survival, Overall survival

DOI: https://doi.org/10.21203/rs.3.rs-76152/v1

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Abstract

Background Medullary thyroid carcinoma (MTC) accounts for 1% -2% of thyroid cancer in the United States based on the latest Surveillance, Epidemiology, and End Results (SEER) data, this study aimed to construct a comprehensive predictive nomogram based on various clinical variables in MTC patients who undergo total thyroidectomy and neck lymph nodes dissection.

Methods Data regarding 1237 MTC patients who undergo total thyroidectomy and neck lymph nodes dissection from 2004 to 2015 were obtained from the SEER database. Univariate and multivariate Cox regression analyses were used to screen for meaningful independent predictors. These independent factors were used to construct a nomogram model, a survival prognostication tool for 3- and 5-year overall survival and cancer-specific survival among these MTC patients.

Result A total of 1237 patients enrolled from the SEER database were randomly divided into the training group (n = 867) and the test group (n = 370). Univariate and multivariate Cox regression analyses were used to identify meaningful independent prognostic factors (P <0.05). Tumor size, age, metastasis status, and LNR were selected as independent predictors of overall survival (OS) and cancer-specific survival (CSS). Finally, two nomograms were developed, the predicted C-index of overall survival (OS) and cancer-specific survival (CSS) rate in the training group were 0.828 and 0.904, respectively. The predicted C-index of overall survival (OS) and cancer-specific survival (CSS) rate in the test group were 0.813 and 0.828.

Conclusion Nomograms constructed by using various clinical variables can make more comprehensive and accurate predictions for MTC patients who undergo total thyroidectomy and neck lymph nodes. These predictive nomograms help identify postoperative high-risk MTC patients and facilitate patient counseling on clinical prognosis and follow-up.

Background

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignant tumor derived from parafollicular cells, accounting for 1% -2% of thyroid cancer in the United States based on the latest Surveillance, Epidemiology, and End Results (SEER) data(1). 25% of MTCs are of hereditary origin, which is related to the RET proto-oncogene, most occurs as part of multiple endocrine neoplasia (MEN) 2 syndrome, and the remaining occur as sporadic forms(2). The guidelines of the National Comprehensive Cancer Network (NCCN) and the American Thyroid Association (ATA) recommend total thyroidectomy and varied levels of lymphadenectomy for MTC patients. Total thyroidectomy and bilateral central neck dissection are the standard surgical procedure for MTC in sporadic or hereditary form. Patients with primary tumor size greater than 1 cm or central lymph nodes metastasis may be considered for modified ipsilateral radical cervical lymphadenectomy(1). MTC accounts for 14% of all thyroid cancer-related deaths, and the 10-year survival rate of patients whose tumors are limited to the glands is 95.6%, its 10-year survival rate drops to 75.5% when cervical lymph node metastasis exists, patients with distant metastases had the worst prognosis and only 40% of patients can survive for 10 years(3). The current prognosis evaluation
depends on the American Journal of Cancer Society (AJCC) TNM staging system, of which other variables that may be significant for determining the outcome of individual patients are not considered. Allen S. Ho et al. proposed a nomogram model combined seven indicators, including postoperative calcitonin, vascular infiltration (VI), clinical TNM status, age, and gender to predict the survival prognosis of MTC with a C-index 0.77 in a small sample size(4). The Surveillance, Epidemiology, and End Results (SEER) is a public database collecting cancer diagnosis, treatment, and survival data for approximately 30% of the US population, and provides researchers with enough clinical information for free(5, 6). Nomogram is a scientific tool which is convenient for clinicians to use two or more variables to estimate clinical events and have been applied in the prognostic system of many malignant tumors(7). In this study, we assessed MTC patients who undergo total thyroidectomy and neck lymph nodes dissection registered between 2004 and 2015 in the SEER database and develop validated nomograms for overall survival (OS) and cancer-specific survival (CSS) of MTC patients.

Methods

Patients and Data collection

The data were extracted from the SEER database using the SEER*Stat software (version 8.3.6; National Cancer Institute, USA). The patients were limited to being diagnosed with MTC and undergo total thyroidectomy and neck lymph nodes dissection between January 1, 2004, and December 31, 2015. We extracted the following clinical information from the database: age at diagnosis, race(Black, White, Other), sex, year of diagnosis, histologic type, clinical TNM stage, tumor size, tumor extension, number of nodules, surgery of primary site, number of removal lymph nodes, the number of regional lymph nodes by pathological findings, the number of positive lymph nodes (pLNs), survival time, cause of death, survival status, and based on the regional lymph nodes by pathological findings and the numbers of positive lymph nodes (pLNs) of each patient, we calculated the lymph node ratio (LNR). The exclusion criteria were set as follows after obtaining data: (1) patients with missing or unknown clinical information, (2) patients with survival time less than 1 month, and (3) patients without local lymph node dissection. Finally, 1237 patients were collected from the SEER database based on the inclusion and exclusion criteria. According to the two optimal cut-off values of every variable, patients were divided into three groups and the survival curves of the three groups were significantly different. X-tile software was used to find out the optimal cut-off values for age, tumor size, the number of regional lymph nodes by pathological findings, the number of pLNs, and LNR. We divided the age into the following three groups based on optimal cut-off values: <47, 48–71, and > 72 years; the optimal cut-off values of tumor size were 20 and 40 mm, the optimal cut-off values of the number of regional lymph nodes by pathological findings were 12 and 32, the optimal cut-off values of the number of positive lymph nodes (pLNs) were 1 and 16, the optimal cut-off values of lymph node ratio (LNR) were 19% and 49%. Clinical staging is based on the 8th edition of the AJCC staging manual. We randomly divided them into a training cohort (n = 867) and a test cohort (n = 370) in the ratio 7:3. The endpoints of this study are overall survival (OS) and cancer-specific survival (CSS), OS refers to the period from the time of surgery to the death of any cause
or the date of the last follow-up, while CSS was calculated from the time of operation to the date of cancer-related death or the time of last follow-up(8). We calculated the 3-year and 5-year survival rates of OS and CSS at the same time.

**Statistical Analysis**

Summary statistics tables used to describe demographic and clinical characteristics of the training cohort and test cohort, data of continuous and categorical variables are presented as frequencies with percentages using Word 2016 for Windows. Survival time was defined as the time (in months) from surgery to death, last follow-up, or December 31, 2015. The optimal cut-off values of age, tumor size, the number of regional lymph nodes by pathological findings, pLNs, and LNR were evaluated by using the X-tile software as described previously. Univariate Cox regression analysis was applied to evaluate independent survival-related factors for Overall survival (OS) and Cancer-specific survival (CSS) in the retrospective data. In a multivariate analysis, the Cox proportional hazards regression model was applied for the categorical variables identified as significant in the univariate Cox regression analysis. The intensity of the association between each predicted categorical variables and survival was expressed as a hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated at the same time. The Cox regression analysis was performed by using Statistical Product and Service Solutions (SPSS) version 26.0, and P-values < 0.05 were considered statistically significant. The nomograms were internally and externally validated in training and test cohorts respectively, the Harrell's concordance index(C-index), receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to evaluate the exact prognostic performance of nomograms, the values of C-index and AUC closer to 1 implied a better predictive accuracy. The verification curve can reflect the consistency between the prediction and actual nomograms. The C-index, ROC, Nomograms, and the verification curve of the training cohort were formulated and adjusted by using R version 3.6.3 in the RStudio environment, the C-index and AUC were also calculated in the test cohort to further evaluate the performance of the nomogram.

**Ethical approval**

SEER data are deidentified before release and do not contain any personally identifying information. As the data is publicly available, no ethical approval is required. We received permission to access the research data file in the SEER program from the National Cancer Institute, USA.

**Results**

**Demographic and clinical characteristics of MTC patients**

A total of 1237 patients registered with MTC who undergo total thyroidectomy and neck lymph nodes dissection between 2004 and 2015 were enrolled from the SEER database based on the inclusion and exclusion criteria, all patients were divided into the training group (n = 867) and test group (n = 370). Their basic information on demographic and clinical characteristics are listed in Table 1. In the training Cohort, the number of patients in training group aged <48, 48-71, and >71 were 299 (34.5%), 468 (54.0%), and
There were 67 (7.7%) black people, 740 (85.4%) white people, and 60 (6.9%) other races (American Indians, Alaska Natives, and Asian/Pacific Islanders). Female and male patients were 479 (55.2%) and 388 (44.8%), respectively. The number of patients with solitary and multiple nodules was 589 (67.9%) and 278 (32.1%). Those with tumor size < 20, 20–40, and > 40 mm were, respectively, 381 (43.9%), 318 (36.7%), and 168 (19.4%). The numbers of people with clinical staging stage of T1a, T1b, T2, T3a, T3b, T4a, T4b were 168 (19.4%), 175 (20.2%), 204 (23.5%), 118 (13.6%), 125 (14.4%), 52 (6.0%), and 25 (2.9%). The number of patients with No, N1a, N1b status was 391 (45.1%), 169 (19.5%), and 307 (35.4%). Those with metastatic status M0 and M1 were, respectively, 810 (93.4%) and 57 (6.6%). The number of those people with 1-3 or >3 cervical regional lymph nodes removed were 158 (18.2%) and 709 (81.8%), respectively. The number of MTC patients with <12, 12-32, and >32 regional lymph nodes by pathological findings were 367 (42.3%), 253 (29.2%), 247 (28.5%). The number of 0, 1-16, and >16 positive lymph nodes were 393 (45.3%), 378 (43.6%), 96 (11.1%). The number of those with LNR ratio <19%, 19% -49%, and >49% were 514 (59.3%), 191 (22.0%), 162 (18.7%), respectively (Table 1). The information of variables in the test cohort can be seen in Table 1, the proportion of each variable is basically identical with the training cohort. In the training cohort, except for race, clinical T status, surgery scope of regional lymph nodes, the number of regional lymph nodes by pathological findings, other variables were significantly meaningful (P <0.05) in the univariate Cox regression analysis for OS. Categorical variables defined as having a significant association with OS on univariate analysis were studied in a Cox proportional hazards model, there are four significant meaningful predictors: tumor size, age, metastasis status, and LNR in this multivariate Cox regression for OS (Table 2). In the univariate Cox regression analysis for CSS, the following seven variables were found to be significantly associated with the CSS of the primary cohort: age, sex, tumor size, clinical T status, metastasis status, the number of positive lymph nodes (pLNs) and LNR were significantly meaningful (P<0.05). In the multivariate Cox regression for CSS, the following 4 variables were identified to construct the Cox proportional hazards regression model, namely tumor size, age, metastasis status, and LNR (Table 3).

### Development and Validation of the Nomograms for OS and CSS

The nomograms of CSS and OS were formulated in the training cohort based on the results of multivariate analysis and Cox proportional hazards regression model, some non-significant predictors and variables with minor effects were excluded. Finally, tumor size, age, metastasis status, and LNR were selected to construct the nomogram of OS as having the highest predictive accuracy. Tumor size, age, metastasis status, and LNR were used to develop the nomogram for CSS according to the multivariate analysis outcomes. We performed Internal validation to correct the bias of overfitting that outcomes from testing on the same patient population. The C-index applied to evaluate the prediction accuracy of the nomogram, the C-index of OS and CSS were, respectively, 0.828 and 0.904, representing a relatively satisfactory predictive accuracy. The ROC was plotted in Figure 1, the 3-year survival AUC of the nomogram was 0.834 and 0.906 in OS and CSS, and the 5-year survival AUC of the nomogram was 0.84...
and 0.915 in OS and CSS (Figure 2). The calibration curve demonstrated that the values of 3- and 5-year OS and CSS predicted by the nomogram were consistent with actual outcomes (Figure 3). Kaplan-Meier methods were used to analyze the survival curve of meaningful independent predictors about CSS in the training cohort (Figure 4). The external validation cohort was applied to evaluate the predictive performance of the nomogram, the demographic information and clinical characteristics of the test cohort are listed in Table 1, the C-index were 0.828 and 0.813 for CSS and OS in the test cohort, the ROC was plotted in Figure 5, the AUC of 3- and 5-year survival were 0.942 and 0.948 in CSS, the AUC of 3- and 5-year survival was 0.804 and 0.832 in OS. The validation of both nomograms demonstrates satisfactory agreement with predicted values.

**Discussion**

MTC accounts for 3 %–5 % of thyroid cancers worldwide. The proportion of MTC dropped to 1% -2% due to a significant increase in the relative incidence of PTC in the United States during the past three decades(1). It is a rare histological subtype with poor prognosis compared with PTC and FTC, more than 50% of MTC patients are deemed with recurrence through biopsy examination after surgery within 10 years, distant metastases occur in 10% of patients despite locoregional control(4, 9). Study found that the extent of surgical resection is an independent predictor of survival outcome for MTC patients, and primary surgical regions less than total thyroidectomy and the decreased survival rate were related. Therefore, total thyroidectomy and cervical lymph nodes dissection based on the clinical and pathologic results became a standard surgical treatment method for patients with sporadic or hereditary MTC according to the latest guideline of ATA and NCCN(1, 3).

The X-tile software have been used to find out the optimal cut-off points of continuous variables that affect the prognosis of tumor survival(10). In current study, the X-tile software calculated the ages of 48 and 71 as the optimal cut-off points to distinguish survival rates of MTC patients. Similarly, the optimal cut-off values of tumor size were 20 and 40 mm, and 12 and 32 regional lymph node dissection was turning point in the survival rate. The optimal cut-off points for the number of positive lymph nodes (pLNs) are 1 and 16. The best cut-off points for LNR are 19% and 49% according to the results of X-tile analysis. After the COX univariate and multivariate regression, we designed a model that systematically considers multiple variables based on the independent predictor of CSS and OS including age, tumor size, metastasis status, and LNR.

Age is an independent predictor for MTC confirmed by many studies(11). Patients age >65 had a decreased survival rate and the risk of death increases by 5.2% for each additional year(3). Previous study found that tumor size >4 cm had significantly worse survival outcome compared to those diameter ≤4 cm(12). The results of this study verified the previously established conclusions that lesion size is associated with a decreased survival trend(13, 14). Distant metastases are often found in involved organs and metastases could occur in multiple organs such as lungs, liver, and bone simultaneously(2). Compared with patients whose lesions confined to the gland, patients with regional metastases have a 2.69 times higher risk of disease related death, while the patients with distant metastases have a 4.47
times higher risk of disease related death(3). The 5-year survival rate after the diagnosis of distant metastasis was 26% and the 10-year survival rate was 10% according to the result of a retrospective study(11, 15). The positive rate of lymph nodes (LNR) is the ratio of the number of positive lymph nodes (pLNs) to the total number of lymph nodes examined by pathology, it has been recognized as an independent prognostic factor for the survival of breast cancer, pancreatic cancer, gastric cancer, colon cancer, uterine and ovarian cancer. Tingyin Jiang et al(16) demonstrated that LNR could predict survival outcomes and provide guidance and suggestions on the prognosis after an operation in patients with stage IV MTC and the optimal cut-off value of LNR to predict OS was 76.5%.

Nomograms have been widely used in clinical work as a reliable predictive tool, it solves the complexity of balancing different factors through statistical modeling so that patients and doctors can quantify risk based on the chart. At present, nomograms are used in the prognosis analysis of various malignant tumors, such as thyroid, breast, prostate, etc(17, 18). According to the statistical analysis results of 249 MTC patients at Memorial Sloan-Kettering Cancer Center from1986 to 2010. Allen S. Ho et al. concluded that age, gender, postoperative calcitonin, perivascular invasion, pathologic T status, pathologic N status, and M status have the highest prediction accuracy for MTC specific mortality. The final nomogram with a C-index 0.77 was constructed based on the seven variables(4). The limitation of this retrospective study is that the data collection sample size is too small, resulting in controversy for this nomogram. A study that included 1252 MTC patients with active follow-up from 1973 to 2002 in the SEER database found that age at diagnosis and stage of disease were the strongest predictors for survival(3). However, nomogram was not constructed in that study.

We construct the nomogram based on the four prognostic factors mentioned above. To our knowledge, this is the first nomogram with excellent predictive performances to investigate the prognostic value of MTC patients who underwent total thyroidectomy and cervical dissection. In our study, to build a refined nomogram, some controversial factors such as radiotherapy and chemotherapy were not taken into account. Treatment with radioactive iodine(\[^{131}\text{I}\]) is meaningless on account of medullary carcinoma cells that originated from C cells that do not absorb \[^{131}\text{I}\]. A single-center experience indicates that adjuvant radioisotope therapy was not sensitive to the medullary carcinoma cells unless the MTC patient accompanied by histological subtypes of papillary or follicular(19). Besides, previous studies based on the seer database showed that 57% of all MTC patients who receiving adjuvant radioisotope treatment had extrathyroidal invasion and local infiltration and found that the addition of radiation will reduce the survival rate even for patients with regional and distant metastasis(3). Similarly, cytotoxic chemotherapy treatment has little effect on MTC(20). As for the efficacy of newer tyrosine kinase inhibitors, more clinical trials are needed. the information on patients’ adjuvant chemotherapy and molecular targeted therapy was not collected by the SEER database.

The strength of our study is that there were the large number of cases included, and the observation and follow-up time was longer. More influencing predictors were evaluated by an appropriate statistical analysis method and a model with clinical application value was constructed based on these independent predictors. The variables of our nomogram are easily available in clinical data. Of course,
our research also has limitations. First, our study failed to include a biochemical evaluation with serum calcitonin and carcinoembryonic antigen (CEA) levels owing to SEER’s lack of information regarding biochemical examination results, both of them are recognized independent factors which predict the outcome. Meanwhile, our nomogram did not include calcitonin and CEA doubling times. Second, classic surgical approach for cervical lymph nodes including unilateral or bilateral central lymphadenectomy, modified lymphadenectomy, radical lymphadenectomy. We cannot evaluate the effectiveness of particular surgical techniques on account of this level of surgical detailed information that is not available in the SEER. Finally, familial MTC, multiple endocrine neoplasia (MEN)-2A or 2B, genetic RET mutation status, and other information about familial MTC cannot be obtained in the SEER database, which prevents us from independently assessing any predictor related to it. It should be noted that our nomograms have not been validated external datasets, and it is necessary to use other databases for calibration in the future. We anticipate physicians to use nomograms to evaluate prognosis, combined with clinical variables such as calcitonin, CEA, or the latest research results such as tumor necrosis and high mitotic rate(21), and expect them to confirm the output of the tool.

Conclusion

In summary, this study used routine clinical data to built the first nomogram model of 3- and 5-year CSS and OS among MTC patients who undergo total thyroidectomy and neck lymph nodes dissection. The nomogram provides a convenient prognostication model for the clinical practice of surgeon, and facilitate patient counseling on clinical prognosis and follow-up.

Abbreviations

OS
overall survival; CSS:cancer-specific survival; MTC:Medullary thyroid carcinoma; SEER:Surveillance, Epidemiology, and End Results; MEN:Multiple endocrine neoplasia; NCCN:National Comprehensive Cancer Network; ATA:American Thyroid Association; AJCC:American Journal of Cancer Society; VT:vascular infiltration; pLN:the number of positive lymph nodes; LNR:lymph node ratio; SPSS:Statistical Product and Service Solutions; C-index:Concordance index; AUC:area under the ROC curve.

Declarations

Acknowledgment
the work has not been published previously, and not under consideration for publication elsewhere.

Authors' contribution
LC and YW contributed equally as first authors of this manuscript and finished the manuscript. Other authors contributed to the data collection and analysis. All authors have read and approved the final submitted manuscript.
Funding

No funding was obtained for this study.

Availability of data and materials

All data were generated from the SEER database, This data can be found here: https://seer.cancer.gov/data/.

Consent for publication

Not applicable

Competing interests

All authors declare that no conflict of interest exists in the submission of this manuscript.

Ethics approval and consent to participate

Not applicable

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Tables
Table 1 Baseline demographic and clinical characteristics of MTC patients who undergo total thyroidectomy and neck lymph nodes dissection.

| Variables          | Training Cohort(%) (n = 867) | Test Cohort(%) (n = 370) |
|--------------------|-------------------------------|--------------------------|
| Age(y)             |                               |                          |
| < 48               | 299(34.5)                     | 137(37.0)                |
| 48–71              | 468(54.0)                     | 184(49.7)                |
| > 71               | 100(11.5)                     | 49(13.3)                 |
| Race               |                               |                          |
| Black              | 67(7.7)                       | 28(7.6)                  |
| White              | 740(85.4)                     | 319(86.2)                |
| Other              | 60(6.9)                       | 23(6.2)                  |
| Sex                |                               |                          |
| Male               | 388(44.8)                     | 141(38.1)                |
| Female             | 479(55.2)                     | 229(61.9)                |
| Number of nodules  |                               |                          |
| Solitary           | 589(67.9)                     | 260(70.3)                |
| Multiple           | 278(32.1)                     | 110(29.7)                |
| Tumor size(mm)     |                               |                          |
| <20                | 381(43.9)                     | 162(43.8)                |
| 20–40              | 318(36.7)                     | 151(40.8)                |
| >40                | 168(19.4)                     | 57(15.4)                 |
| T                  |                               |                          |
| T1a                | 168(19.4)                     | 83(22.4)                 |
| T1b                | 175(20.2)                     | 77(20.8)                 |
| T2                 | 204(23.5)                     | 92(24.9)                 |
| T3a                | 118(13.6)                     | 48(13.0)                 |

Abbreviations: Number of removal LNs, Number of removal lymph nodes; Total LNs, the number of regional lymph nodes by pathological findings; pLNs, Positive lymph nodes; LNR, lymph node ratio.
|                | Training Cohort(%) | Test Cohort(%) |
|----------------|--------------------|----------------|
| **T3b**        | 125 (14.4)         | 42 (11.4)      |
| **T4a**        | 52 (6.0)           | 17 (4.6)       |
| **T4b**        | 25 (2.9)           | 11 (3.0)       |
| **N**          |                    |                |
| N0             | 391 (45.1)         | 200 (54.1)     |
| N1a            | 169 (19.5)         | 48 (13.0)      |
| N1b            | 307 (35.4)         | 122 (33.0)     |
| **M**          |                    |                |
| M0             | 810 (93.4)         | 354 (95.7)     |
| M1             | 57 (6.6)           | 16 (4.3)       |
| **Number of removal LNs** |       |                |
| 1–3            | 158 (18.2)         | 70 (18.9)      |
| ≥ 4            | 709 (81.8)         | 300 (81.1)     |
| **Total LNs**  |                    |                |
| 0–11           | 367 (42.3)         | 178 (48.1)     |
| 12–32          | 253 (29.2)         | 89 (24.1)      |
| 33–90          | 247 (28.5)         | 103 (27.8)     |
| **pLNs**       |                    |                |
| 0              | 393 (45.3)         | 200 (54.1)     |
| 1–16           | 378 (43.6)         | 130 (35.1)     |
| 17–73          | 96 (11.1)          | 40 (10.8)      |
| **LNR**        |                    |                |
| < 19.0%        | 514 (59.3)         | 250 (67.6)     |
| 19.0%-49.0%    | 191 (22.0)         | 60 (16.2)      |
| > 49.0%        | 162 (18.7)         | 60 (16.2)      |

Abbreviations: Number of removal LNs, Number of removal lymph nodes; Total LNs, the number of regional lymph nodes by pathological findings; pLNs, Positive lymph nodes; LNR, lymph node ratio.
Table 2
Univariate and Multivariate Cox regression analysis of Overall survival (OS) in the training cohort.

| Characteristics   | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|
|                   | HR                  | 95% CI                | P-value  | HR                  | 95% CI                | P-value  |
| **Age (y)**       |                     |                       |          |                     |                       |          |
| < 48              | Reference           | Reference             |          | Reference           | Reference             |          |
| 48–71             | 6.965               | 3.363–14.425          | ≤ 0.001* | 7.635               | 3.675–15.863          | ≤ 0.001* |
| > 71              | 21.564              | 10.108–46.003         | ≤ 0.001* | 22.406              | 10.384–48.346         | ≤ 0.001* |
| **Race**          |                     |                       |          |                     |                       |          |
| Black             | Reference           |                       |          |                     |                       |          |
| White             | 0.764               | 0.421–1.388           | 0.377    |                     |                       |          |
| Other             | 0.574               | 0.215–1.531           | 0.268    |                     |                       |          |
| **Sex**           |                     |                       |          |                     |                       |          |
| Male              | Reference           |                       |          |                     |                       |          |
| Female            | 0.571               | 0.402–0.811           | 0.002*   |                     |                       |          |
| **Number of nodules** |                 |                       |          |                     |                       |          |
| Solitary          | Reference           |                       |          |                     |                       |          |
| Multiple          | 0.620               | 0.410–0.939           | 0.024*   |                     |                       |          |
| **Tumor size (mm)** |                   |                       |          |                     |                       |          |
| < 20              | Reference           |                       |          | Reference           |                       |          |
| 20–40             | 2.429               | 1.512–3.902           | ≤ 0.001* | 2.369               | 1.468–3.824           | ≤ 0.001* |
| > 40              | 5.347               | 3.338–8.567           | ≤ 0.001* | 3.178               | 1.948–5.186           | ≤ 0.001* |
| **T**             |                     |                       |          |                     |                       |          |
| T1a               | Reference           |                       |          |                     |                       |          |
| T1b               | 1.362               | 0.597–3.106           | 0.463    |                     |                       |          |
| T2                | 2.050               | 0.976–4.309           | 0.058    |                     |                       |          |

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *means P < 0.05.
|                  | Univariate analysis | Multivariate analysis |
|------------------|---------------------|-----------------------|
| **T3a**          | 3.505               | 1.659–7.404           |
|                  |                     | ≤ 0.001*              |
| **T3b**          | 4.787               | 2.337–9.808           |
|                  |                     | ≤ 0.001*              |
| **T4a**          | 9.006               | 4.236–19.148          |
|                  |                     | ≤ 0.001*              |
| **T4b**          | 6.743               | 2.736–16.615          |
|                  |                     | ≤ 0.001*              |
| **N**            |                     |                       |
| **N0**           | Reference           |                       |
| **N1a**          | 2.452               | 1.500–4.007           |
|                  |                     | ≤ 0.001*              |
| **N1b**          | 3.017               | 1.966–4.628           |
|                  |                     | ≤ 0.001*              |
| **M**            |                     |                       |
| **M0**           | Reference           | Reference             |
| **M1**           | 6.117               | 3.984–9.392           |
|                  |                     | ≤ 0.001*              |
|                  | 3.936               | 2.488–6.227           |
|                  |                     | ≤ 0.001*              |
| **Number of removal LNs** |                   |                       |
| 1–3              | Reference           |                       |
| ≥ 4              | 1.117               | 0.709–1.762           |
|                  |                     | 0.632                 |
| **Total LNs**    |                     |                       |
| 0–11             | Reference           |                       |
| 12–32            | 1.268               | 0.820–1.960           |
|                  |                     | 0.285                 |
| 33–90            | 1.645               | 1.088–2.486           |
|                  |                     | 0.018*                |
| **pLNs**         |                     |                       |
| 0                | Reference           |                       |
| 1–16             | 2.357               | 1.551–3.584           |
|                  |                     | ≤ 0.001*              |
| 17–63            | 4.246               | 2.557–7.050           |
|                  |                     | ≤ 0.001*              |

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *means P < 0.05.
| LNR              | Univariate analysis | Multivariate analysis |
|------------------|---------------------|-----------------------|
| < 19.00%         | Reference           | Reference             |
| 19.00%-49.00%    | 2.092               | 1.326–3.301           | 0.002* | 1.603 | 1.006–2.554 | 0.047* |
| > 49.00%         | 4.441               | 2.966–6.649           | ≤0.001* | 3.006 | 1.974–4.577 | ≤0.001* |

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; *means P < 0.05.
Table 3
Univariate and Multivariate Cox regression analysis of Cancer-specific survival (CSS) in the training cohort.

| Characteristics       | Univariate analysis | Multivariate analysis |
|-----------------------|---------------------|-----------------------|
|                       | HR  | 95% CI       | P-value | HR  | 95% CI       | P-value |
| Age(y)                |     |               |         |     |               |         |
| < 48                  |     | Reference     |         |     | Reference     |         |
| 48–71                 | 4.02 | 1.685–9.557   | 0.002*  | 4.97 | 2.058–11.992 | ≤ 0.001* |
| > 71                  | 10.83 | 4.223–27.761  | ≤ 0.001* | 13.40 | 5.004–35.863 | ≤ 0.001* |
| Race                  |     |               |         |     |               |         |
| Black                 |     | Reference     |         |     | Reference     |         |
| White                 | 0.84 | 0.336–2.115   | 0.715   |     |               |         |
| Other                 | 0.23 | 0.027–1.975   | 0.181   |     |               |         |
| Sex                   |     |               |         |     |               |         |
| Male                  |     | Reference     |         |     | Reference     |         |
| Female                | 0.57 | 0.337–0.973   | 0.039*  |     |               |         |
| Number of nodules     |     |               |         |     |               |         |
| Solitary              |     | Reference     |         |     | Reference     |         |
| Multiple              | 0.84 | 0.472–1.507   | 0.565   |     |               |         |
| Tumor size(mm)        |     |               |         |     |               |         |
| < 20                  |     | Reference     |         |     | Reference     |         |
| 20–40                 | 5.02 | 2.053–12.287  | ≤ 0.001* | 4.48 | 1.813–11.048  | ≤ 0.001* |
| > 40                  | 11.46 | 4.712–27.846  | ≤ 0.001* | 5.56 | 2.223–13.895  | ≤ 0.001* |
| T                     |     |               |         |     |               |         |
| T1a                   |     | Reference     |         |     | Reference     |         |
| T1b                   | 1.06 | 0.149–7.529   | 0.953   |     |               |         |
|                  | Univariate analysis |                          | Multivariate analysis |
|------------------|---------------------|--------------------------|-----------------------|
|                  | T2                  | 4.081                    | 0.881–18.904          | 0.072                 |
|                  | T3a                 | 5.536                    | 1.150–26.655          |                       | 0.033*                 |
|                  | T3b                 | 13.180                   | 3.014–57.640          | ≤                     | 0.001*                 |
|                  | T4a                 | 29.048                   | 6.518–129.457         | ≤                     | 0.001*                 |
|                  | T4b                 | 27.548                   | 5.691–133.349         | ≤                     | 0.001*                 |
| N                | N0                  | Reference                |                       |                       |                       |
|                  | N1a                 | 5.847                    | 2.388–14.313          | ≤                     | 0.001*                 |
|                  | N1b                 | 7.443                    | 3.236–17.122          | ≤                     | 0.001*                 |
| M                | M0                  | Reference                | Reference             |                       |                       |
|                  | M1                  | 12.854                   | 7.382–22.384          | ≤                     | 0.001*                 | 6.694 3.690–12.145    | ≤ 0.001* |
| Number of removal LNs | 1–3                | Reference                |                       |                       |                       |
|                  | ≥ 4                 | 1.015                    | 0.520–1.981           |                       | 0.965                  |
| Total LNs        | 0–11                | Reference                |                       |                       |                       |
|                  | 12–32               | 1.295                    | 0.665–2.518           |                       | 0.447                  |
|                  | 33–90               | 1.79                     | 0.958–3.343           |                       | 0.068                  |
| pLNs             | 0                   | Reference                |                       |                       |                       |
|                | Univariate analysis |          | Multivariate analysis |          |
|----------------|---------------------|----------|-----------------------|----------|
|                |                     |          |                       |          |
| **1–16**       | 5.737               | 2.506–13.131 | ≤ 0.001*              |          |
| **17–63**      | 11.917              | 4.823–29.444 | ≤ 0.001*              |          |
| **LNR**        |                     |          |                       |          |
| < 19.00%       | Reference           |          |                       | Reference|
| 19.00%–49.00%  | 4.536               | 2.117–9.720 | ≤ 0.001*              | 3.287    | 1.493–7.235 | 0.003* |
| > 49.00%       | 9.875               | 4.868–20.034 | ≤ 0.001*              | 5.874    | 2.794–12.352 | ≤ 0.001* |