Nomograms Predict Survival in Patients with Anaplastic Thyroid Carcinoma

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Background: Anaplastic thyroid carcinoma (ATC) is a very rare, highly lethal malignant cancer. Our aim in this study was to develop nomograms that predict survival in ATC patients.

Material/Methods: ATC incidence and mortality were assessed via joinpoint regression analysis of 567 ATC patients selected from the Surveillance, Epidemiology, and End Results 18 Registries Research database. Predictive models were established via univariate and multivariate Cox regression analysis of potential risk factors and used to produce nomograms. Performance of the nomograms in terms of discrimination ability and calibration was evaluated by determining the concordance index (C-index) and by generating calibration plots, respectively.

Results: The incidence and mortality rates for ATC increased from 2000 to 2015 according to the collected data (p<0.05). Two nomograms were constructed based on 2 predictive models: nomogram 1 considered age, tumor size, and metastasis (all before surgery), and nomogram 2 considered age, tumor size, metastasis, surgery, and extrathyroidal extension (all after surgery). Both nomogram 1 (C-index, 0.6803; 95% confidence interval, 0.6517–0.7089) and nomogram 2 (C-index, 0.7064; 95% confidence interval, 0.6783–0.7345) had good discrimination ability. The validated C-index values were 0.6783 and 0.7029 for nomogram 1 and 2, respectively. The observed values were in agreement with the calibration curves.

Conclusions: Nomogram 1 can assist in preoperative prediction of survival time in ATC patients, whereas nomogram 2 can provide additional outcome-related information.

MeSH Keywords: General Surgery • Nomograms • Thyroid Neoplasms

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Background

Anaplastic thyroid carcinoma (ATC) is a very rare, highly lethal, malignant tumor [1]. The reported median survival time for ATC varies from 3 to 10 months, with few long-term survivors [2–5]. Retrospective analyses have identified age, sex, tumor size, and tumor extent as prognostic factors for survival [6–8]. However, no model is available for predicting survival status according to baseline characteristics. Herein, we describe the generation of such a model using data from the Surveillance, Epidemiology, and End Results (SEER) database.

Material and Methods

Data collection. The SEER 18 Registries Research database for incidence-based mortality was used for analyzing ATC incidence and mortality from 2000 to 2015. The adjusted age-standardized incidence rates stratified by sex served as the dependent variable in joinpoint regression analyses performed using SEER software [9].

The SEER 18 Registries Research Data and Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub database were used for analysis of ATC survival outcomes [10]. This database consists of a retrospectively analyzed ATC cohort; case recording began in 1973 and ended in 2015. The cohort comprised 1642 patients with anaplastic carcinoma (8021/3: Carcinoma, anaplastic, NOS). After excluding patients with incomplete medical histories, 567 patients were included in our survival study (Figure 1).

Patient and disease characteristics, including sex, age at the time of definitive diagnosis, tumor size, multifocality, extrathyroidal extension (ETE), lymph node metastasis (LNM), distant metastasis, surgery, race, follow-up time, and survival status, were recorded for further study.

Statistical analysis. Categorical variables were expressed as numbers and percentages, whereas continuous variables were expressed as medians and ranges. Survival rates were estimated using the Kaplan-Meier method with the log-rank test. Univariate Cox regression analysis was used to assess the crude association between each of the potential predictors and long-term survival. Factors significantly associated with survival were included in the multivariate Cox regression analysis, which was performed using model 1 (before surgery) or model 2 (after surgery). p<0.05 was considered significant in two-tailed tests.

Nomograms were developed to visualize the results of the survival prediction models, and their performance in terms of discrimination and calibration was determined. Discrimination was evaluated using the concordance index (C-index), which quantifies the predictive ability of the model; the scores range from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and scores <0.5 indicating no concordance [11]. Calibration (i.e., the agreement between the actual frequencies and predicted percentages) was represented graphically (calibration curves). The closer the calibration curve to the ideal curve, the better the agreement [11].

Kaplan-Meier analysis with the log-rank test was performed using GraphPad software (Prism 7 for Windows, version 7.00, 2016). Univariate and multivariate Cox regression analyses were conducted using SPSS software (IBM SPSS Statistics for Windows, version 23, IBM Corp., Armonk, NY, USA, 2016). Nomograms were generated and validated using R software, version 3.5.3 (http://www.r-project.org/). Our analytic approach is diagrammed in Figure 1.

Results

Tendencies of incidence and mortality in ATC patients

The incidence and mortality rates for the entire ATC cohort increased from 2000 to 2015 according to the data retrieved from the SEER database (p<0.05) (Figure 2). The rates for men and women were similar to those for all patients (p>0.05).

Clinical characteristics of the patients

The median age of the 567 patients in the study was 70 years (range, 26–100 years), and the female-to-male ratio was 1.601 (349 women and 218 men). The total median survival duration...
Figure 2. Joinpoint analysis for anaplastic thyroid carcinoma. (A) Incidence rate. (B) Mortality rate. APC – annual percent change.

Table 1. Clinical characteristics of anaplastic thyroid carcinoma.

| No. patients (%) | Sex | Male | Female |
|------------------|-----|------|--------|
| 349 (61.6)       |     | 218 (38.4) |
| Age at diagnosis (years old) [Median, Range] | 70.26–100 |
| Tumor size (mm) [Median, Range] | 60.3–152 |
| Multifocality | Multifocal tumor | 126 (22.2) |
|                 | Solitary tumor | 441 (77.8) |
| ETE | No | 122 (21.5) |
| LNM | N0 | 270 (47.6) |
|      | N1 | 297 (52.4) |

M | M0 | 351 (61.9) |
| M1 | 216 (38.1) |

Operation | Yes | 329 (58.0) |
| No | 238 (42.0) |

Race recode | White | 465 (82.0) |
| Asian or Pacific Islander | 60 (10.6) |
| Black | 42 (7.4) |

ETE – extrathyroidal extension; LNM – lymph node metastasis; M – metastasis.

was 5 months, with 1-, 3-, and 5-year survival rates of 17.6%, 7.9%, and 5.1%, respectively. Table 1 shows the baseline clinical characteristics of the patients.
Table 2. Univariate analysis.

|                              | Median Survival (mo) | 1-Year Survival (%) | HR (95%CI)       | P     |
|------------------------------|----------------------|---------------------|------------------|-------|
| **Sex**                      |                      |                     |                  |       |
| Female                       | 6                    | 29.4                |                  |       |
| Male                         | 6                    | 26.0                | 1.001 (0.906–1.105) | 0.989 |
| Age (years old)*             | –                    | –                   | 1.021 (1.012–1.029) | <0.001|
| Age (years old)              |                      |                     |                  |       |
| <55                          | 8                    | 86.4                |                  |       |
| 55–75                        | 5                    | 36.9                | 1.318 (0.956–1.816) | 0.091 |
| ≥75                          | 3                    | 26.5                | 1.810 (1.303–2.513) | <0.001|
| **Multifocality**            |                      |                     |                  |       |
| Solitary tumor               | 6                    | 29.2                |                  |       |
| Multifocal tumor             | 7                    | 23.8                | 1.040 (0.795–1.360) | 0.579 |
| ETE                          |                      |                     |                  |       |
| No                           | 8                    | 43.2                |                  |       |
| Yes                          | 4                    | 23.8                | 1.620 (1.262–2.079) | <0.001|
| **LNM**                      |                      |                     |                  |       |
| N0                           | 7                    | 34.1                |                  |       |
| N1                           | 5                    | 22.1                | 1.382 (1.138–1.679) | 0.001 |
| **M**                        |                      |                     |                  |       |
| M0                           | 7                    | 36.2                |                  |       |
| M1                           | 4                    | 12.9                | 2.079 (1.701–2.540) | <0.001|
| Operation                    |                      |                     |                  |       |
| No                           | 4                    | 13.7                |                  |       |
| Yes                          | 7                    | 36.5                | 0.458 (0.375–0.559) | <0.001|
| **Race recode**              |                      |                     |                  |       |
| Asian or Pacific Islander    | 5                    | 20.4                |                  |       |
| Black                        | 7                    | 18.4                | 0.906 (0.575–1.429) | 0.672 |
| White                        | 6                    | 30.3                | 0.797 (0.585–1.085) | 0.150 |
| Tumor size (mm)              |                      |                     |                  |       |
| ≤10                          | 31                   | 66.7                |                  |       |
| 10–20                        | 4                    | 42.9                |                  |       |
| 20–30                        | 7                    | 41.7                |                  |       |
| 30–40                        | 7                    | 39.7                |                  |       |
| 40–50                        | 6                    | 37.3                |                  |       |
| 50–60                        | 6                    | 34.8                |                  |       |
Table 2 continued. Univariate analysis.

| Median Survival (mo) | 1-Year Survival (%) | HR (95%CI) | P     |
|----------------------|----------------------|------------|-------|
| 60–70                | 4                    | 22.1       |       |
| 70–80                | 5                    | 33.3       |       |
| 80–90                | 4                    | 38.6       |       |
| 90–100               | 3                    | 25.6       |       |
| >100                 | 1                    | 19.4       |       |
| Tumor size (mm)      |                      |            |       |
| ≤60                  | 7                    | 31.3       |       |
| >60                  | 4                    | 19.6       | 1.605 (1.321–1.950) <0.001 |

* Not classified into different groups. CI – indicates confidence interval; ETE – extrathyroidal extension; LNM – lymph node metastasis; M – metastasis. Statistically significant <0.05.

Univariate analysis

Univariate analysis showed older age, larger tumor size, ETE, LNM, distant metastasis, and lack of surgery as risk factors for overall survival (Table 2, Figure 3). Sex, multifocality, and race did not significantly impact overall survival.

Multivariate analysis

Two models were developed for multivariate analysis of the factors that were significantly associated with survival in univariate analysis. Model 1 included 3 preoperative factors: age, tumor size, and distant metastasis (Figure 4). Model 2 included 5 postoperative factors: age, tumor size, distant metastasis, ETE, and surgery.

Nomograms for ATC patients. Nomograms 1 and 2 were developed based on models 1 and 2, respectively. They were used to visualize the outcome results (Figure 5). As an example, a patient had ATC according to preoperative assessment (model 1). He was 60-years-old (5 points), with a tumor size of 4 cm (1.5 points), and no distant metastasis (0 points). According to nomogram 1, his 1-, 3-, and 5-year survival rates were approximately 51%, 41%, and <40%, respectively, before surgery (total points, 6.5). If surgery was insufficient (3.1 points) and ETE was present (1.7 points), his 1-year survival rate was <30% according to nomogram2 (total points, 11.3).

Validation of the nomogram predictions

The C-index values for nomogram 1 and 2 were 0.6803 (95% confidence interval [CI], 0.6517–0.7089) and 0.7064 (95% CI, 0.6783–0.7345), respectively; this indicates that both models had good discrimination ability. The bias-corrected C-index according to bootstrap analysis with 1000 resamples was 0.6783 for nomogram 1 and 0.7029 for nomogram 2. The calibration plots for the nomograms show that the predicted models conformed with the observed reality (Figure 6).

Discussion

Thyroid cancer is the most prevalent endocrine malignancy, and its incidence has increased considerably in many regions [12,13]. Although ATC accounts for only 2% of all thyroid carcinomas [14], its incidence and mortality rates have risen between 2000 and 2015 according to the SEER database used in this study (Figure 2). Using the SEER 13 database, Mao and Xing showed a significant increase in ATC incidence between 1992 and 2012 [15]. In contrast, the retrospective analysis by Keinan et al. showed a decrease between 1980 and 2012 [13]; this difference mainly reflects the use of data from different databases [13].

Although there are many treatments for ATC, including surgery, systemic therapy (radiation and chemotherapy), and supportive care during active therapy [1,16,17], the mortality rate for ATC is still very high [2–5]. In this study, the median overall survival duration was 5 months, which is consistent with the findings of other studies [2–5].

To accurately evaluate the survival durations of ATC patients, assessment of a combination of clinicopathological characteristics is crucial. In this study, 2 nomograms were developed after performing systematic analyses. Nomogram 1 considered 3 factors (tumor size, age, and metastasis before surgery) and nomogram2 considered 5 factors (tumor size, age, metastasis, surgery, and ETE after surgery). Using these nomograms,
we identified older age, larger tumor size, distant metastasis, lack of surgery, and ETE as risk factors for survival of ATC patients. Previous studies also reported associations of these factors with unfavorable outcomes [1,8,18,19]. For example, Kim et al. reported that age >60 years, tumor size ≥7 cm, and greater tumor extension predicted worse disease-related mortality rates [8]. However, the exact risk according to age and tumor size is unknown.

Surgery is essential for prolonging the survival of ATC patients [2,20], and in agreement with this observation, we found that surgery was a protective factor for patients in our study. ETE occurs quite frequently in ATC, contraindicating tumor resection and worsening prognosis [4]. The percentage of ATCs with ETE was 42.1% in the study by Chen et al. [10] and 78.5% in our study. Although distant metastasis is less common in ATC than ETE, it is more deadly, accounting for 47.5–90% of

**Figure 3.** Kaplan-Meier survival curves for prognostic factors. Curves for age (A), ETE (B), LMN (C), distant metastasis (D), surgery (E), and tumor size (F) are shown. ETE – extrathyroidal extension; LMN – lymph node metastasis; N0 – without lymph node metastasis; N1 – with lymph node metastasis; M0 – without distant metastasis; M1 – with distant metastasis.
### Table 1

| Variables  | Adjusted HR (95% CI) | p Value   | Variables  | Adjusted HR (95% CI) | p Value   |
|------------|----------------------|-----------|------------|----------------------|-----------|
| M          | 2.243 (1.828–2.753)  | <0.001    | ETE        | 1.369 (1.059–1.789)  | 0.016     |
| Tumor size | 1.113 (1.068–1.160)  | <0.001    | Operation  | 1.752 (1.426–2.153)  | <0.001    |
| Age        | 1.026 (1.018–1.035)  | <0.001    | M          | 1.964 (1.594–2.421)  | <0.001    |

### Table 2

| Variables  | Adjusted HR (95% CI) | p Value   |
|------------|----------------------|-----------|
| Tumor size | 1.093 (1.047–1.140)  | <0.001    |
| Age        | 1.024 (1.015–1.032)  | <0.001    |

### Figure 4.

(A, B) Forest plots for multivariate Cox analysis. ETE – extrathyroidal extension; M – distant metastasis.

### Figure 5.

Nomograms based on models 1 and 2. (A) Nomogram 1. (B) Nomogram 2.
Figure 6. Calibration plots for the nomograms. (A) 1-year survival. (B) 3-year survival. (C) 5-year survival. The dotted lines correspond to nomogram 1 and the solid lines correspond to nomogram 2.
Pre-operation assessment have completed

Evaluating the probability of 1-year survival status according to nomogram 1

≥70%

30–70%

<30%

Considering operation

Operation recommended

No

Yes

Evaluating the probability of 1-year survival status according to nomogram 2

≥70%

30–70%

<30%

Systemic therapy and supportive care during active therapy

Combining actual situation

Positive postoperative review

Figure 7. Process for combining nomograms to determine the appropriate treatment for anaplastic thyroid carcinoma patients.

ATC-related deaths [10]. The metastatic rate in our study was 38.1%. Given the impact of multiple factors on ATC prognosis, using a combination of these factors for assessing survival is a sensible approach for clinicians.

We recommend that clinicians use the nomograms presented in our study when making treatment decisions. Before applying the nomograms, an exhaustive preoperative assessment of the patient should be made via thyroid ultrasound, cervical computed tomography, and positron emission tomography/computed tomography. If the preoperative assessment indicates ATC, clinicians should estimate survival times using nomogram 1 to determine whether surgery is needed. If so, the outcomes can be further assessed using nomogram 2. This process is outlined in Figure 7.

The discrimination abilities of nomogram 1 and nomogram 2 were good. The validated C-index values for nomograms 1 and 2 were 0.6783 and 0.7029, respectively, in a bootstrap analysis of 1000 resamples. Moreover, the predicted models were in accordance with the observed values according to calibration curves generated via bootstrap analysis of 1000 resamples.

A strength of our study is the use of joinpoint regression analysis to determine the tendencies of incidence and mortality. Furthermore, to the best of our knowledge, this is the first study to present a multi-factor survival model of ATC with nomograms. Moreover, internal validation was achieved via bootstrap analysis with 1000 resamples. Limitations of this study include the lack of external validation, owing to the limited number of cases, and exclusion of basic information, such as life habits and body mass indices. Lastly, the effects of beam radiation and chemotherapy on survival of ATC patients were not addressed.

Conclusions

Predictive nomograms are user-friendly, providing a visual representation of the survival status of ATC patients, and they can help clinicians select the most appropriate treatments for these patients.

Conflicts of interest

None.
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